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EFFECTIVENESS AND SAFETY OF ORAL SEDATION IN ADULT PATIENTS UNDERGOING DENTAL PROCEDURES: A SYSTEMATIC REVIEW

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ABSTRACT

Objectives The management of anxious patients undergoing dental procedures remains a challenge in clinical practice. The evidence available on the effectiveness and safety of oral sedation in adults is scarce. This study evaluated the effectiveness and safety of oral sedation in patients undergoing dental procedures.

Design Systematic review.

Methods Randomized clinical trials (RCTs) comparing the oral use by adults of benzodiazepines and other medications versus placebo or other oral agents were eligible. A search of the Cochrane (CENTRAL), MEDLINE (via Ovid), EMBASE (via Ovid), CINAHL (via Ovid) and among other was conducted, without restriction of languages or date of publication, up to March 2020. Primary outcomes included anxiety, sedation, treatment satisfaction, pain and adverse effects. Secondary outcomes included heart rate, respiratory rate, blood pressure and oxygen saturation and patient cooperation during intervention. Reviewers, independently and in pairs, assessed each citation for eligibility, performed data extraction and the risk of bias. A narrative synthesis of the data was provided.

Results RCTs (n=327 patients) assessed the use of benzodiazepines (n=9) and herbal medicines (n=3). Results showed no reports of pain after use of midazolam 15mg or placebo; good satisfaction with treatment after use of midazolam 7.5mg or clonidine 150µg; and reduced anxiety with the use of alprazolam 0.5 and 0.75mg. Midazolam 15mg promoted greater anxiety reduction than *Passiflora incarnata* L 260mg, while *Valeriana officinalis* 100mg and *Erythrina mulungu* 500mg were more effective than placebo. Larger number of patients reported adverse effects with the use of midazolam 15mg. Diazepam 15mg and *V. officinalis* 100mg promoted less change in heart rate and blood pressure than placebo.

Conclusion Given the limitation in the findings regarding the quality of studies and different comparisons between interventions, further RCTs can confirm data on the effectiveness and safety of oral sedation in dentistry.

Protocol registration: PROSPERO CRD42017057142.

Strengths and limitations of this study

• We performed a comprehensive systematic review of the published and grey literature to identify randomised clinical trials that evaluated the effectiveness and safety of oral sedation, in patients undergoing dental surgical procedures.

• Anxiety can lead to dental treatment avoidance with consequent exacerbation of the oral health of phobic patients. Knowing which drugs are effectives on control of anxiety can contribute in patient compliance for dental treatment.

• Adverse effects with the use of oral sedatives are negative outcomes in dentistry that should be avoided. Estimating the risk rate of such events in patients treated with oral sedation may contribute to the decision-making process regarding conscious sedation.

• This study assessed the use of benzodiazepines and herbal medicines for oral sedation. In general, such drugs demonstrated benefits for some outcomes, with midazolam being the drug that demonstrated the highest number of reported adverse effects.

• The quality of studies and different comparisons between the interventions were a limiting factors. Then further RCTs can confirm data on the effectiveness and safety of oral sedation in dentistry.

INTRODUCTION

Anxiety during dental treatment can cause stress and discomfort for patients, and also lead to treatment avoidance with consequent exacerbation of the oral health of phobic patients.[1 2]

In this context, effective control of anxiety plays a pivotal role in patient compliance for dental treatment. The use of conscious sedation is an important strategy for behavioural management of patients who suffer from anxiety over dental treatment.[3]

Conscious sedation is an approach that uses one or more drugs to produce a state of central nervous system (CNS) depression, while maintaining verbal contact with the patient throughout the procedure.[4] The sedation level should be such that the patient remains conscious and is capable of readily understanding and responding to verbal instructions or tactile stimulation.[5]

Indications for use of conscious sedation include a diagnosis of anxiety and dental phobia, prolonged or traumatic dental procedures, medical conditions

potentially aggravated by stress and that can reduce the patient´s ability to cooperate, such as special needs.[6]

Additionally, release of endogenous catecholamine's can increase the load on the cardiovascular system in patients with a history of angina, whereas asthmatic patients can present stress-induced acute episodes of breathing difficulty induced by stress. These are among some of the profiles of patient that can benefit from conscious sedation to reduce the risk of exacerbation. This also applies to patients who may present special risk and, in these cases, the risk-benefit should be determined according to the severity of the disease.[7]

Oral sedation is a relatively accessible means for dental surgeons to control patient anxiety. However, as for any approach, oral sedation can have inherent limitations due to the pharmacokinetics of the orally administered drug, such as delayed and variable onset of action.[8] Moreover, drug interventions to provide conscious sedation should have a sufficient safety margin to preclude loss of consciousness.[9]

Given these characteristics, benzodiazepines are widely used in oral sedation to induce a state of anxiolysis in dental procedures.[10] These drugs are also among the most commonly prescribed and employed for this purpose worldwide. [5 8 11 12]

Although benzodiazepines have a similar mechanism of action, their pharmacokinetic characteristics differ, which in turn are a key factor for selecting the best option to suit the patient´s profile.[13] The different options for oral sedation in dentistry include midazolam, diazepam and lorazepam as mainstream drugs, although alprazolam, temazepam and oxazepam have also been used.[8]

Few studies have synthesized the available evidence on the effectiveness and safety of oral sedation in adults undergoing dental procedures. Systematic review evaluated the safety of the use of drugs for sedation administered via oral, intranasal, sublingual, intramuscular and intravenous routes in adults undergoing dental procedures. However, this study search involved only a single database, failed to perform data extraction in pairs and independently, and did not assess the risk of bias or quality of the evidence of the outcomes found.[10]

Another systematic review investigated the use of midazolam in dental surgical procedures.[14] Of the 10 studies included in the review, only 3 addressed oral use, while the others combined drugs administered orally and by other

routes. The hypothesis of this study is that conscious oral sedation is safe for use in dental procedures. The gap in knowledge on the use of drugs for oral sedation in dentistry prompted the present systematic review that determined the effectiveness and the safety of drugs used for oral sedation in adult patients undergoing dental surgical procedures.

METHODS

Protocol registration

The protocol of this systematic review was published [15] and registered on the PROSPERO – *International Prospective Register of Systematic Reviews* (registration number CRD42017057142) at the site address: (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=57142).

Patient and Public Involvement

No patient involved.

Eligibility criteria of studies

Inclusion criteria

Participants: adults requiring dental surgical procedures, such as dental extraction, surgery for orthodontic purposes, removal of residual roots and third molars, dental implants and other dental surgical interventions.

Intervention: at least one of the groups used oral sedation with benzodiazepines or other drugs (e.g. herbal medicines).

Comparator: placebo group or other drug administered by oral route.

Study: randomized clinical trials (RCTs).

Exclusion criteria

Studies involving adults with respiratory diseases, patients with contraindications for benzodiazepine use, pregnant and/or breastfeeding women and those with a history of allergy were not included. Studies combining administration of different drugs for oral sedation were also excluded.

Outcomes assessed

Primary outcomes

The studies had to report at least one of the following outcomes: pain, sedation, satisfaction with treatment, anxiety and adverse effects.

Secondary outcomes

Secondary outcomes collected were: heart rate, respiratory rate, blood pressure and oxygen saturation and patient cooperation during the intervention (as described by authors).

Search method for identifying studies

Electronic database search

The search strategy sought in the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), which includes Dentistry and Oral Health Group's Specialized Register, MEDLINE (via Ovid), EMBASE (via Ovid), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (via Ovid), Lilacs (Scielo) and the Capes database (https://catalogodeteses.capes.gov.br/catalogo-teses/#!/), without restriction on publication date, with search encompassing articles published up to March 2020.

Other reference search sources

For review articles, the reviewers (CCB and JOA) analysed the reference list or citation in the text to verify and identify other possible eligible studies. Whenever necessary, main authors and/or pharmaceutical companies involved in the production of the drugs were contacted for information on additional trials.

Search strategy

The search was conducted using MeSH (Medical Subject Headings) terms for each oral surgical procedure (such as oral surgery, dental extraction and dental implant), benzodiazepines (and its synonyms) and terms to search for other drugs. The search strategy for MEDLINE (via Ovid) was adapted for each database (Appendix A).

Study eligibility

Four reviewers (JDOA and CCB, CCG and NKA), working in pairs and independently, selected potentially relevant titles and abstracts and applied the

eligibility criteria. Full texts of potentially eligible articles were obtained. Similarly, the reviewers checked the eligibility of each study and the disagreements were resolved by consensus. When necessary, a third reviewer achieved consensus (RHLM or LCL).

Data extraction

The same reviewers (JDOA and CCB, CCG and NKA), working in pairs and independently, were calibrated based on data extraction from 3 articles. Subsequently, the reviewers extracted patient data, methods, interventions and outcomes. This extraction was done according to the instructions manual devised by the principal author of this review. Disagreements were resolved by consensus and, when necessary, arbitrated by a third reviewer (RHLM or LCL).

Risk of bias

A modified version of the Cochrane collaboration approach for assessing risk of bias was used.[16 17] The same reviewers, again in pairs and independently, evaluated the risk of bias for each clinical trial according to randomization; allocation concealment; blinding of patient, health professional and outcomes assessors; incomplete outcome data, selective outcome reporting and major baseline imbalance characterizing the sample.

The same reviewers attributed the standard answers “definitely yes”, “probably yes”, “probably no” and “definitely no” for each domain; with “definitely yes” and “probably yes” denoting a low risk of bias and “definitely no” and “probably no” attributing a high risk of bias.[18] Similarly, the reviewers resolved disagreements by consensus. Disagreements were resolved by consensus and, when necessary, arbitrated by a third reviewer (RHLM or LCL).

Data synthesis and analysis of quality of evidence

The quality of the evidence was planned to be assessed for each outcome reported using the GRADE system and summarized with the aid of the Software GRADE PRO.[19 20] However, as meta-analysis could not be performed, the GRADE was not produced. A narrative synthesis of the findings was carried out.

RESULTS

Search strategy results

A total of 3,669 publications were retrieved, of which 49 were included for full-text selection. After application of the eligibility criteria, 10 RCTs were included in the review (Figure 1). The characteristics of the studies included are given in Appendix B and the studies excluded are listed in Appendix C.

Description of studies included

The 10 RCTs involved 327 patients undergoing oral surgery and comprising approximately 58% women. Most of the RCTs evaluated the use of benzodiazepines (n=9) and 3 studies assessed the use of herbal medicines for oral sedation, predominantly used in dental extraction procedures. The majority of the studies were by Brazilian researchers and conducted between 2011 and 2017. Only 1 study was funded by the pharmaceutical industry (Table 1).

Risk of bias (Figure 2)

Random sequence generation

One study failed to report sufficient data on the randomization process, precluding any assessment and therefore exhibited selection bias.[21-27] Stated that a random sequence of patients in the groups was generated, but did not report details on the process used.

Allocation concealment

The studies[22 24 28] guaranteed that the random sequence generation of participants was unpredictable, since the envelopes handed to participants were sealed and coded. By contrast, the clinical trials[21 23 25 27 29] did not guarantee allocation concealment. The clinical trials[26 30] provided insufficient information on the random sequence generation process employed.

Blinding of participants and personnel

Two studies[22 23] described clearly that the blinding of participants and personnel was ensured and unlikely to have been lost, and thus had no performance bias. The remaining studies[21 24-30] stated they were double-blind, but provided no further details. Consequently, these studies were deemed “probably yes” and considered as low risk of bias.

Blinding of outcome assessors

In 3 studies[22 27 28] the blinding of outcome assessors was performed, making it unlikely that blinding was lost. The studies[24 30] stated that the professionals were blinded, but it was unclear whether they were blinded for outcome collection. The other studies[21 23 25 26 29] did not report this information, indicating detection bias.

Incomplete outcomes

For one study[23] it was not possible to judge whether incomplete outcome reporting occurred. The remaining studies made clear whether there was loss of follow-up of participants or otherwise.

Selective outcome reporting

Of the studies selected, only one study[22] reported information on the primary outcome “pain”, while none of the studies reported “patient cooperation”. Other study[30] recorded the protocol allowing confirmation that there was no selective outcome reporting. For the other publications, although the study protocol was not recorded, evidence suggests these studies reported all the desired outcomes.

Other sources of bias

Only one study[22] cited the source of funding. Other studies declared there was no funding.[21 22 25-28 30] The remaining studies[23 24 29] did not report sufficient information to assess the presence of other sources of bias.

Outcomes assessed

The primary and secondary outcomes reported by the studies are given in Table 2. Due to differences between drugs used across groups, a meta-analysis of the data could not be performed and results were expressed in the form of a narrative synthesis. None of the studies reported the sedation outcome and secondary outcomes of respiratory rate and patient cooperation with treatment.

Reporting of primary outcomes

Pain

Only one study reported the pain outcome.[22] This crossover design RCT assessed 30 patients undergoing bilateral surgical extraction of third molars assigned to midazolam 15 mg (single dose, 45 minutes prior to dental procedure) or placebo groups. The results revealed that none of the patients in either group reported pain and that duration of surgical procedure did not differ between the two groups.

Satisfaction with treatment

One RCT, crossover, reported level of patient satisfaction with the treatment.[29] In the study, 12 patients undergoing bilateral surgical extraction of third molars were allocated to receive the following interventions 1 hour before the procedure: Group I – midazolam 7.5 mg and Group II – clonidine 150 ug. The level of satisfaction with the surgical procedure was determined on a Visual Analogue Scale (VAS) with ratings ranging from "no satisfaction" (0%) and "complete satisfaction" (100%). Around 77% of the patients receiving midazolam were satisfied compared to 75% of those using clonidine.

Anxiety

Five studies reported anxiety levels.[23 25 27 28 30]

In one placebo-controlled RCT, 48 participants undergoing dental extraction were allocated into 4 groups (n=12 per group): Group I – alprazolam 0.25 mg; Group II – alprazolam 0.50 mg; Group III – alprazolam 0.75 mg; Group IV – placebo. Anxiety was assessed using the Dental Anxiety Scale (DAS) (which categorizes participants into not anxious, slightly anxious, fairly anxious and very anxious); the Oral Surgery Confidence Questionnaire (OSCQ) (containing 11 items rated from 0 – not at all confident to 9 – extremely confident), and by the Interval Scale of Anxiety Response (ISAR) (consisting of a 90mm vertical line labelled with descriptors alongside at intervals determined according to estimated magnitude: “calm, relaxed”, “a little nervous”, “tense, upset”, “afraid”, “very afraid”, “panicked” and “terrified”. The proportion of individuals reporting feeling fairly to very anxious during the oral surgery decreased with increasing doses of alprazolam.[23]

In a double-blind, placebo-controlled RCT[25], 30 participants undergoing dental implant placement surgery were allocated into 3 different groups (n=10 per group) that received the following interventions 1 hour prior to the procedure: Group I – diazepam 10 mg; Group II – lorazepam 1 mg; Group III – placebo. Anxiety was measured based on vital signs recorded (blood pressure and heart rate) and by responses on the Corah Dental Anxiety Scale. No significant difference was found between the groups for vital signs or use of the scale.

An RCT with a crossover design allocated 40 participants undergoing mandibular third molar extraction into 2 groups (n=40), each receiving interventions 30 minutes prior to the procedures: Group I – *P. incarnata* 260 mg and Group II – midazolam 15 mg. The Corah Dental Anxiety scale was used before and after the surgical procedure. Both medications proved effective for controlling anxiety and safe for conscious sedation, although midazolam 15 mg promoted a greater reduction in anxiety compared with *Passiflora incarnata* L. 260 mg.[27]

Performed an RCT with a crossover design, allocating 20 participants undergoing bilateral third molar extraction into 2 groups (n=20), each receiving interventions 1 hour before the procedure: Group I – *V. officinalis* 100 mg and Group II – placebo. Anxiety was measured by the DAS and physiological parameters. *V. officinalis* was more effective for controlling anxiety than placebo.[30]

Erythrina mulungu (500 mg, single dose, 1 hour before dental procedure, intervention group) was assessed in a crossover design RCT involving 30 patients undergoing bilateral extraction of impacted thirds molars versus placebo. Anxiety was determined based on Corah Dental Anxiety Scale score and physiological parameters (heart rate and oxygen saturation). The results showed no differences in physiological parameters between the 2 groups. The study findings also showed that volunteers with higher anxiety levels tended to prefer *E. mulungu*.[28]

Adverse effects

Six studies collected information on adverse effects.[21-23 27 29 30]

The studies reporting the percentage of participants experiencing adverse effects are described in Table 3. In general, most participants exhibited adverse

effects. Reported only the number of adverse effects and therefore its results were not included in the table.[27]

Did not specify the adverse effect by group and consequently this result was not included. The most commonly observed adverse effect in the study was anterograde amnesia associated with use of alprazolam (at doses of 0.25 mg, 0.50 mg and 0.75 mg) compared to placebo.[23]

The number of reports of adverse effects is shown in Table 4. In general, a higher number of adverse effects were associated with the use of midazolam compared to *P. incarnata* and placebo, where the most reported events were drowsiness, muscular relaxation and dizziness.[22 27]

Reported only this outcome.[21] The study allocated 82 patients undergoing outpatient dental surgery to use of: Group I – placebo, Group II – trazodone 25 mg, Group III – trazodone 50 mg, and Group IV – diazepam 15 mg. Comparison of reports of adverse effects for trazodone versus diazepam revealed that the latter drug was associated with more effects. The main effects reported were drowsiness, vertigo and cognitive impairment (Table 3). In addition, the number of individuals in use of diazepam reporting adverse effects was also higher (Table 2).

Reporting of secondary outcomes

The secondary outcomes reported were heart rate, blood pressure and oxygen saturation.

Heart rate was reported by 5 studies. Found no significant differences between the groups studied.[27 28] Found that *V. officinalis* promoted less change in heart rate compared to placebo.[30] Performed an RCT with a crossover design, allocating 15 participants undergoing implant placement to receive either midazolam 15 mg or placebo, 1 hour before the procedure. The use of midazolam proved ineffective as a pre-medication anxiolytic for preventing myocardial arrhythmias.[24] Similarly, found no difference in heart rate in the diazepam 15 mg group compared to the other groups.[21]

Blood pressure was reported by 5 studies. Found no statistically significant differences in the parameters systolic and diastolic blood pressure for the groups assessed.[27-29] In the study, *V. officinalis* use was associated with less change in blood pressure compared to placebo.[30] In the study, a reduction in

blood pressure was observed after use of diazepam 15 mg, but this difference was not statistically significant compared to the other groups.[21]

Oxygen saturation was reported by 3 studies. Found no difference for this parameter compared to the other groups.[27 28] In a RCT with a crossover design, allocated 20 participants undergoing periodontal surgery to receive diazepam 5 mg or 10 mg doses (according to body weight, a tablet the night before and 1 hour before surgery) and placebo.[26] No significant differences in oxygen saturation were reported in either of the groups.

DISCUSSION

Main findings and literature comparison

This study evaluated the available evidence on the effectiveness and safety of the use of oral sedation in adults undergoing dental procedures. The review included 10 RCTs involving patients undergoing mainly tooth extractions. The majority of the RCTs evaluated the use of benzodiazepine class drugs for oral sedation, where the most commonly used was midazolam. Most of the studies were conducted in Brazil, none of which met all of the evaluation criteria for risk of bias. The main methodological flaws were related to randomization and allocation concealment.

The heterogeneity of the interventions precluded the performing of a meta-analysis for any of the outcomes assessed. Studies found addressed the primary outcomes pain, satisfaction with treatment, anxiety and adverse effects.[21-23 25 27-30]

There were no reports of pain in patients who used midazolam 15 mg or placebo.[22] For satisfaction with treatment, no difference was found between midazolam 7.5 mg and clonidine 150 µg.[29]

In general, alprazolam (0.5 and 0.75 mg),[23] midazolam 15 mg, *P. incarnata* 260 mg,[27] *V. officinalis*[30] and E. mulungu[28] were considered effective for controlling anxiety.

The results revealed a higher number of reports of adverse effects associated with midazolam use,[22 27] followed by diazepam.[21] In addition, a greater number of patients reported adverse effects for these two benzodiazepines. However, these findings should be interpreted with caution, given that the high number of reports might be related to the larger number of participants in these

studies. Moreover, these findings are based on reports by only one study, where lack of comparability between studies hampers any meaningful conclusion on the safest intervention.

There was no difference in the number of patients exhibiting adverse effects after using midazolam 7.5 mg and clonidine 150 ug,[29] but more adverse effects were reported in the group receiving midazolam 15 mg than in the placebo group. These results suggest that the increase in midazolam dose may be associated with a rise in the number of adverse effects.

Previous systematic reviews on this subject[10 14] could not be used to compare against the findings of the present study, because the RCTs included in these reviews were not restricted to oral route, combining different drugs and routes of administration. In addition, these reviews failed to report most of the outcomes assessed in the present study.

Included 21 RCTs assessing sedation safety by any administration route, in patients undergoing dental procedures. Ten of the studies included were RCTs, but none of these were included in the present review for having used a combination of drugs or alternative routes of administration other than oral. The cited review found midazolam to be the most used drug, irrespective of administration route. Although the authors stated the drug appeared to be safe for sedation of dental patients, the risk of bias of the studies was not taken into account, and further clinical trials were suggested to confirm the findings.[10]

Investigated the anxiolytic effect of midazolam in dental surgery, regardless of administration route.[14] Of the 10 studies reviewed, 3 involved oral administration, of which only 1 RCT was included in the present study,[29] since the other clinical trials used a combination of different drugs or alternative routes of administration.

With regard to secondary outcomes, no significant differences in heart rate or blood pressure were evident upon comparing *E. mulungu* to placebo,[28] *P. incarnata* to midazolam,[27] midazolam to clonidine,[29] diazepam to placebo or to trazodone.[21] However, the use of *V. officinalis* was associated with less change for these parameters relative to placebo.[30] There was no difference in oxygen saturation for use of *E. mulungu* versus placebo,[28] *P. incarnata* versus midazolam[27] or for diazepam versus placebo.[26] In the literature searched, no secondary studies comparing these outcomes were found.

Study strengths and limitations

The present study was carried out with methodological rigor and included an evaluation of the risk of bias not performed in previous systematic reviews on the topic.[10 14] Strengths of the present study include its explicit eligibility criteria, broad extensive database search, and study selection by reviewers working both independently and in pairs.

The primary studies included were a limiting factor for the findings of this review owing to the methodological quality of the RCTs, the non-reporting of clinical outcomes and different comparator groups, precluding a meta-analysis. Another notable factor was the heterogeneous method of reporting the anxiety outcome among studies, where some used validated scales, while others measured anxiety based on physiological parameters such as heart rate and blood pressure.

It is also noteworthy that the vast majority of the RCTs (90%) failed to take into consideration the patient´s anxiety level as a study inclusion criterion. Was one of the exceptions, reporting that patients with higher anxiety levels tended to prefer the herbal medicine.[28] This information is important in that, according to the literature, oral sedation can help most patients with mild to moderate levels of fear and anxiety, but may be ineffective in patients with high levels of anxiety.[11 31] According to the summary of findings in the present study, this doubt remains.

Implications for clinical practice and research

The findings of this review showed benefits of benzodiazepines use for oral sedation in assessments of out-patient dental surgical procedures. Several herbal-based medicines were also found to be effective in this context. Dental surgeons should devise surgical plans based on the general health status of patients. This requires an in-depth anamnesis in which the patient´s level of anxiety and fear concerning the procedure to be performed is determined, guiding prescription of the most suitable medication.

None of the RCTs evaluated all of the outcomes of interest initially proposed for determining the effectiveness and safety of oral sedation in dental surgical procedures. Also, no comparison of studies was possible due to the different drugs investigated. Therefore, further clinical trials adopting more rigorous methodologies standardized methods for outcome data collection and methodological guidelines should be carried out. Such studies can serve to

validate the findings of the current review and ascertain which benzodiazepines or herbal-based medicines can be considered effective and safe for use in dental procedures.

It is important to point out that, although the findings of this review on the use of benzodiazepines and herbal medicines are somewhat limited, they appear safe under the conditions reported in the RCTs included in the review, i.e. administered orally as a single dose.

The findings of the present study furnish the available evidence on the effectiveness and safety of oral sedation in adults undergoing dental surgical procedures. This evidence can help guide the decision-making process in dental practice, attenuating the risks of anxiety in clinical procedures and of potential adverse effects.

CONCLUSION

The results point to the safety and benefits of the use of alprazolam, midazolam, *P. incarnate, V. officinalis* and *E. mulungu* in controlling anxiety among adult patients undergoing dental intervention. Midazolam proved the most studied, but was also the drug associated with the highest rate of adverse effects. However, in view of the limitations of the study findings concerning the number of studies reviewed, different comparison between the studies, and incomplete outcome reporting; further clinical trials should be conducted to confirm the effectiveness and safety of these drugs.

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Table 1 – Characteristics of studies included (n=10)

Variables	STUDIES (n)	POPULATION (n)
Study population	10	327
Women (n=282)	8	164 (58.2%)
HERBAL MEDICATIONS		
Passiflora incarnata L. 260 mg	1	40
Valeriana officinalis 100 mg	1	10
Erythrina mulungu 500 mg	1	30
BENZODIAZEPÍNES		
Diazepam (5, 10 e 15 mg)	3	49
Alprazolam (0.25, 0.5 and 0.75mg)	1	36
Midazolam (7.5 and 15 mg)	4	97
Lorazepam (1 mg)	1	10
CLINICAL CONDITION		
Dental extraction	6	180
Dental implants	2	45
Other dental surgery	2	102
COUNTRY		
Brazil	5	135
United States of America	1	48
Italy	1	82
Switzerland	1	12
China	1	30
India	1	20
YEAR OF PUBLICATION		
1979-1988	2	112
1989-1998	1	48
1999-2008	0	0
2009-2017	7	167
FUNDED BY INDUSTRY		
Yes	1	30
Not specified	4	157
Not funded	5	140

Table 2 - Primary and secondary outcomes reported by the studies (n= 10 studies)

AUTHOR/YEAR (n= participants)	INTERVENTION GROUP (n= participants)	COMPARATOR GROUP (n= participants)	PRIMARY OUTCOMES	RESULT FOR PRIMARY OUTCOMES	SECONDARY OUTCOMES	RESULT FOR SECONDARY OUTCOMES
Rodrigo & Cheung (1987) Crossover (n=30)	Midazolam 15 mg (n=30)	Placebo (n=30)	Pain	No reports of pain by patients in either group	Not reported	
Studer et al. (2012) Crossover (n=12)	Midazolam 7.5 mg (n=12)	Clonidine 150 ug (n= 12)	Satisfaction with treatment	77% of patients (midazolam group) versus 75% of patients (clonidine group)	Blood pressure	No statistical difference between the groups
Branco, Bassualdo (2012) (n=30)	Diazepam 10 mg (n=10) Lorazepam1 mg (n=10)	Placebo (n=10)	Anxiety	Decreased anxiety compared to baseline levels, but no statistical difference between groups	Not reported	
Coldwell et al. (1997) (n=48)	Alprazolam 0.25 mg (n=12) Alprazolam 0.5 mg (n=12) Alprazolam 0.75 mg (n=12)	Placebo (n=12)	Anxiety	Decrease in number of anxious patients with increasing doses of alprazolam	Not reported	
Dantas et al. (2017) Crossover (n=40)	*Passiflora incarnata L.* 260 mg (n=40)	Midazolam 15 mg (n=40)	Anxiety	Decreased anxiety compared to baseline levels, but no statistical difference between groups	Heart rate Blood pressure Oxygen saturation	No difference between the groups
Pinheiro et al. (2014) (n=20)	*Valeriana officinalis* 100 mg (n=10)	Placebo (n=10)	Anxiety	Herbal medicine was more effective than placebo	Heart rate Blood pressure	Herbal medicine was more effective than placebo No statistical difference between the groups
Silveira-Souto et al. (2014) Crossover (n=30)	*Erythrina Mulungu* 500 mg (n=30)	Placebo (n=30)	Anxiety	Decreased anxiety compared to baseline levels, but no statistical difference between groups	Heart rate Blood pressure Oxygen saturation	No statistical difference between the groups for any of outcomes assessed
Romano et al. (2011) (n=40)	Midazolam 15 mg (n=20)	Placebo (n=20)	Not reported		Heart rate	No statistical difference between the groups
Manani et al. (1979) (n=82)	Diazepam 15 mg (n=19) Trazodone 25 mg (n=20) Trazodone 50 mg (n=21)	Placebo (n=22)	Not reported		Heart rate Blood pressure	No statistical difference between the groups
Shivananda et al. (2014) Crossover (n=20)	Diazepam 5 mg (n=20) Diazepam 10 mg (n=20)	Placebo (n=20)	Not reported		Oxygen saturation	No statistical difference between the groups

Table 3 - Description of studies reporting participants that experienced adverse effects (n= 4 studies)

AUTHOR/YEAR	GROUPS	Number of participants experiencing adverse effects/ total sample (%)
Studer et al. (2012)	Midazolam 7,5 mg	6/12 (50.0)
	Clonidine 150 ug	5/12 (41.6)
Rodrigo & Cheung (1987)	Midazolam 15 mg	17/30 (56.6)
	Placebo	9/30 (30.0)
Pinheiro et al. (2014)	*Valeriana officinalis* 100 mg	9/10 (90.0)
	Placebo	7/10 (70.0)
Manani et al. (1979)	Trazodone 25 mg	12/20 (60.0)
	Trazodone 50 mg	11/21 (52.3)
	Diazepam 15 mg	15/19 (78.9)
	Placebo	12/22 (54.5)

Table 4 - Description of adverse effects reported by the studies (n= 5 studies)

AUTHOR/YEAR	INTERVENTION GROUP (NUMBER OF AE)	DESCRIPTION OF EFFECTS (NUMBER OF AE)	COMPARATOR GROUPS (NUMBER OF AE)	DESCRIPTION OF EFFECTS (NUMBER OF AE)
Dantas et al. (2017)	Midazolam 15 mg (54)	Drowsiness (33), muscular relaxation (11), dizziness (7), gastrointestinal problems (1), amnesia (1) and insomnia (1)	*Passiflora incarnate* L. (32)	Drowsiness (20), muscular relaxation (9), dizziness (2), allergy (1), epistaxis
Manani et al. (1979)	Diazepam 15 mg (36)	Drowsiness (10), vertigo (3) and cognitive impairment (6)	Trazodone 50 mg (28),	Drowsiness (10), vertigo (5), blurred vision (2) cognitive impairment (11)
			Trazodone 25 mg (18)	Drowsiness (15), vertigo (9), blurred vision (6) cognitive impairment (6)
			Placebo (18)	Drowsiness (12), vertigo (1), blurred vision (2) and cognitive impairment (3)
Pinheiro et al. (2014)	*Valeriana officinalis* (16)	Drowsiness (9) and muscular relaxation (7)	Placebo (11)	Drowsiness (7) and muscular relaxation (4)
Rodrigo & Cheung (1987)	Midazolam 15 mg (46)	Drowsiness (17), dizziness (8), memory loss (3), excitability(5), depression (5), nausea (5), vomiting (2) and headache (3)	Placebo (29)	Drowsiness (9), dizziness (4), memory loss, excitability (1), depression (1), blurred vision (1), insomnia (5), hallucinations (1), nausea (4), vomiting (1) and headache (2)
Studer et al. (2012)	Midazolam 7.5 mg (6)	Dizziness (3), nausea, headache and fatigue (1) and cognitive deficit (2)	Clonidine 0.15 mg (6)	Nausea (2), drowsiness (3) and fainting (1)

AE= adverse effects

Figure 1 – Flow chart of study selection process

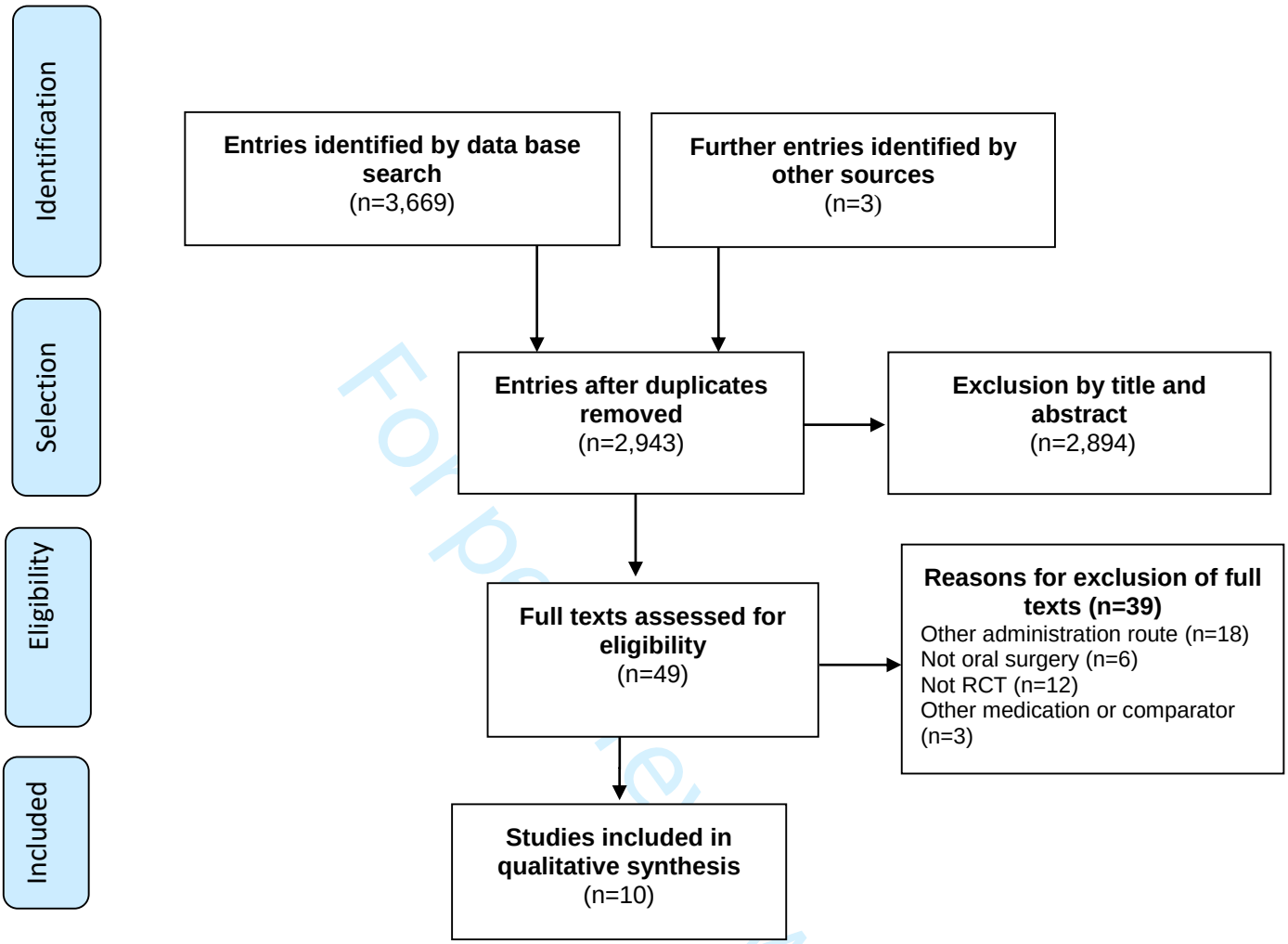

Figure 2 – Consensus of authors on risks of bias of the studies included

APPENDIX A – Search strategy on MEDLINE (via Ovid) database

1.	surgery, maxillofacial.mp. or exp Surgery, Oral/
2.	operative dentistry.mp. or exp Dentistry, Operative/
3.	dentistry, operative.mp. or exp Dentistry, Operative/
4.	prosthesis, surgical dental.mp. or Dental Implants/
5.	prostheses, surgical dental.mp. or exp Dental Implants/
6.	surgical dental prosthesis.mp. or exp Dental Implants/
7.	surgical dental prostheses.mp. or exp Dental Implants/
8.	dental prosthesis, surgical.mp. or exp Dental Implants/
9.	dental prostheses, surgical.mp. or exp Dental Implants/
10.	implant, dental.mp. or exp Dental Implants/
11.	dental implant.mp. or exp Dental Implants/
12.	implants, dental.mp. or exp Dental Implants/
13.	dental implants.mp. or exp Dental Implants/
14.	procedures, maxillofacial.mp. or exp Oral Surgical Procedures/
15.	procedure, maxillofacial.mp. or exp Oral Surgical Procedures/
16.	maxillofacial procedure.mp. or exp Oral Surgical Procedures/
17.	maxillofacial procedures.mp. or exp Oral Surgical Procedures/
18.	exodontics.mp. or exp Surgery, Oral/
19.	procedure, oral surgical.mp. or exp Oral Surgical Procedures/
20.	oral surgical procedure.mp. or exp Oral Surgical Procedures/
21.	surgical procedures, oral.mp. or exp Oral Surgical Procedures/
22.	procedures, oral surgical.mp. or exp Oral Surgical Procedures/
23.	surgical procedures, oral.mp. or exp Oral Surgical Procedures/
24.	oral surgical procedures.mp. or exp Oral Surgical Procedures/
25.	oral surgery.mp. or exp Surgery, Oral/
26.	maxillofacial surgery.mp. or exp Surgery, Oral/
27.	surgery, oral.mp. or exp Surgery, Oral/
28.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29.	benzodiazepinones.mp. or exp Benzodiazepinones/
30.	Benzodiazepinones.mp. or exp Benzodiazepinones/
31.	Alprazolam novopharm brand.mp. or expAlprazolam/
32.	novopharm brand of alprazolam.mp. or exp Alprazolam/
33.	novo alprazol.mp. or exp Alprazolam/
34.	novoalprazol.mp. or exp Alprazolam/
35.	novo-alprazol.mp. or exp Alprazolam/
36.	Alprazolam pfizer brand.mp. or exp Alprazolam/
37.	pfizer brand of alprazolam.mp. or exp Alprazolam/
38.	maleate, midazolam.mp. or exp Midazolam/
39.	midazolam maleate.mp. or exp Midazolam/
40.	midazolam.mp. or exp Midazolam/
41.	effect, antianxiety.mp. or exp Anti-Anxiety Agents/
42.	antianxiety effect.mp. or exp Anti-Anxiety Agents/
43.	effects, anti-anxiety.mp. or exp Anti-Anxiety Agents/
44.	anti anxiety effects.mp. or exp Anti-Anxiety Agents/
45.	anti-anxiety effects.mp. or exp Anti-Anxiety Agents/
46.	effect, anxiolytic.mp. or exp Anti-Anxiety Agents/
47.	anxiolytic effect.mp. or exp Anti-Anxiety Agents/

48.	effects, antianxiety.mp. or exp Anti-Anxiety Agents/
49.	antianxiety effects.mp. or exp Anti-Anxiety Agents/
50.	effects, anxiolytic.mp. or exp Anti-Anxiety Agents/
51.	anxiolytic effects.mp. or exp Anti-Anxiety Agents/
52.	effect, anti-anxiety.mp. or exp Anti-Anxiety Agents/
53.	anti anxiety effect.mp. or exp Anti-Anxiety Agents/
54.	anti-anxiety effect.mp. or exp Anti-Anxiety Agents/
55.	anxiolytics.mp. or exp Anti-Anxiety Agents/
56.	drugs, anti-anxiety.mp. or exp Anti-Anxiety Agents/
57.	anti anxiety drugs.mp. or exp Anti-Anxiety Agents/
58.	anti-anxiety drugs.mp. or exp Anti-Anxiety Agents/
59.	minor tranquillizing agents.mp. or exp Anti-Anxiety Agents/
60.	agents, minor tranquillizing.mp. or exp Anti-Anxiety Agents/
61.	minor tranquilizing agents.mp. or exp Anti-Anxiety Agents/
62.	agents, minor tranquilizing.mp. or exp Anti-Anxiety Agents/
63.	tranquilizing agents, minor.mp. or exp Anti-Anxiety Agents/
64.	agents, anxiolytic.mp. or exp Anti-Anxiety Agents/
65.	anxiolytic agents.mp. or exp Anti-Anxiety Agents/
66.	anti anxiety agents.mp. or exp Anti-Anxiety Agents/
67.	agents, anti-anxiety.mp. or exp Anti-Anxiety Agents/
68.	anti-anxiety agents.mp. or exp Anti-Anxiety Agents/
69.	29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68
70.	69 and 28

APPENDIX B – CHARACTERISTICS OF STUDIES INCLUDED

Study characteristics	**Branco & Bassualdo (2012)**
Method	Randomized double-blind placebo-controlled clinical trial. Allocated 30 participants undergoing dental implant placement surgery into 3 different groups (n=10) to receive a drug 1 hour before procedure. Group I – diazepam 10 mg; Group II – lorazepam 1 mg; Group III – placebo.
Participants	30 participants, both genders, mean age 20-64 years, selected for dental implant placement surgery.
Intervention	Three groups of patients underwent surgery for dental implant placement after oral sedation.
Outcomes	Primary outcomes: anxiety. Secondary outcomes: vital signs (blood pressure, heart rate).
Observations	There were no significant differences in reduction of anxiety or in vital signs pre and post-operatively, only trans-operatively. Effective anxiety control was not demonstrated.

Branco & Bassualdo (2012)	**Deemed risk of bias**	**Support for judgement**
Random sequence generation	High risk	Randomized, although no detailed report on procedure was provided in study description.
Allocation concealment	High risk	No information or scant description on procedures for concealing allocation of patients into groups.

Blinding of participants and personnel	Low risk	Blinding of participants and personnel was done, making it unlikely blinding was lost.
Blinding of outcome assessors	High risk	The study failed to report this information. The outcomes assessed are subject to influence by lack of blinding.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	Low risk	The study protocol is not available, but the study published clearly included all desired outcomes.
Other sources of bias	Low risk	The study appeared to have no other sources of bias.

Study characteristics	**Coldwell et al. (1997)**
Method	Allocated 48 participants undergoing oral surgery for dental extraction into 4 different groups (n=12). Group 1 – alprazolam 0.25 mg; Group 2 – alprazolam 0.50 mg; Group 3 – alprazolam 0.75 mg; Group 4 – placebo.
Participants	48 participants of both genders were selected for surgical dental extraction of 1-4 molars.
Intervention	Four groups of patients submitted to surgical dental extraction after oral sedation.
Outcomes	Primary outcomes: anxiety, adverse effect (anterograde amnesia).
Observations	The study showed that alprazolam caused memory impairment at doses necessary for producing clinically significant anxiolytic effect during oral surgery.

Coldwell et al. (1997)	**Deemed risk of bias**	**Support for judgement**
Random sequence generation	High risk	Randomized, although no detailed report on procedure was provided in study description.
Allocation concealment	High risk	No information or scant description on procedures for concealing allocation of patients into groups.
Blinding of participants and personnel	Low risk	Study not blinded or incomplete blinding, and outcome unaffected by lack of blinding.
Blinding of outcome assessors	High risk	The study failed to report this information. The outcomes assessed are subject to influence by lack of blinding.
Incomplete outcomes	High risk	Insufficient information to judge. The study did not report this information.
Selective outcome reporting	Low risk	The study protocol is not available, but the study published clearly included all desired outcomes.
Other sources of bias	High risk	Insufficient information to judge. The study did not report this information.

Study characteristics	**Dantas et al. (2017)**

Method	Randomized double-blind clinically-controlled crossover trial. Allocated 40 participants undergoing surgical extraction of third molars into 2 groups (n=40) receiving orally administered drug 30 mins before procedure. Group I – *Passiflora incarnata* 260 mg; Group II – midazolam 15 mg.
Participants	40 participants of both genders were selected for third molar extraction.
Intervention	Two groups of patients undergoing surgery for third molar extraction after oral sedation.
Outcomes	Primary outcomes: anxiety, adverse effects. Secondary outcomes: vital signs (blood pressure and heart rate) and oxygen saturation.
Observations	*Passiflora incarnata* promoted similar anxiolytic effect to midazolam, and participants who received the drug had relatively stable blood pressure, heart rate and oxygen saturation.

Dantas et al. (2017)	**Deemed risk of bias**	**Support for judgement**
Random sequence generation	High risk	Randomized, although no detailed report on procedure was provided in study description.
Allocation concealment	High risk	No information or scant description on procedures for concealing allocation of patients into groups.
Blinding of participants and personnel	Low risk	Blinding of participants and personnel was done, making it unlikely blinding was lost.
Blinding of outcome assessors	Low risk	Blinding of outcome assessors was done, making it unlikely blinding was lost.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	Low risk	The study protocol is not available, but the study published clearly included all desired outcomes.
Other sources of bias	Low risk	The study appeared to have no other sources of bias.

Study characteristics	**Manani et al. (1979)**
Method	Randomized double-blind clinically-controlled trial. Allocated 82 patients of both genders, age range 20-50 years, undergoing dental procedures into 4 groups according to drug administered for inducing sedation. Group I – placebo; Group II – trazodone 25 mg; Group III – trazodone 50 mg; Group IV – diazepam 15 mg.
Participants	82 participants of both genders, age range 20-50 years, selected for surgery with oral sedation.
Intervention	O Group I received placebo (Control Group). Group II received trazodone 25 mg. Group III received trazodone 50 mg. Group IV received diazepam 15 mg. All drugs were prepared and distributed in the form of blue capsules to prevent identification of Group by the participants and professionals.
Outcomes	Primary outcomes: anxiety, sedation, adverse effects (drowsiness, vertigo, headache, blurred vision, cold hands and dry mouth). Secondary outcomes: vital signs (blood pressure and heart rate).
Observations	One hour after administration of drug, there was a significant increase in sedation of patients. No adverse effects were observed in patients of control group or trazodone 25 mg group. Patients using diazepam 15 mg or trazodone 50 mg had greater reduction in

	neurovegetative response and higher rate of adverse effects, proving more marked in the group treated with diazepam.

Manani et al. (1979)	**Deemed risk of bias**	**Support for judgement**
Random sequence generation	High risk	Insufficient information on random sequence generation process to allow judgement. No detailed report on procedure was provided in study description.
Allocation concealment	High risk	No information or scant description on procedures for concealing allocation of patients into groups.
Blinding of participants and personnel	Low risk	The study stated that all drugs were placed into identical capsules, thereby ensuring blinding of participants and personnel.
Blinding of outcome assessors	High risk	The study failed to report this information. The outcomes assessed are subject to influence by lack of blinding.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	Low risk	The study protocol is not available, but the study published clearly included all desired outcomes.
Other sources of bias	Low risk	The study appeared to have no other sources of bias.

Study characteristics	**Rodrigo & Cheung (1987)**
Method	Randomized double-blind clinical trial. Allocated 30 participants undergoing surgical extraction of mandibular third molars to receive orally administered drug midazolam 15 mg or placebo, the surgery was carried out by a single operator, randomly, one side per visit.
Participants	30 participants of both genders were selected for surgical removal of third molars.
Intervention	The patients underwent surgical removal of third molars after oral sedation.
Outcomes	Primary outcomes: adverse effects (amnesia, hiccupping, nausea, drowsiness and dizziness) and satisfaction with treatment.
Observations	Midazolam sedation lasted about 45 minutes, produced good operating conditions and stable vital signs with adequate verbal response.

Rodrigo & Cheung (1987)	**Deemed risk of bias**	**Support for judgement**
Random sequence generation	High risk	Randomized, although no detailed report on procedure was provided in study description.

Allocation concealment	Low risk	The pills were sealed and coded in envelopes and thus information on procedures confirmed concealment of allocation of patients into groups.
Blinding of participants and personnel	Low risk	Blinding of participants and personnel was incomplete, but the authors claimed outcome was unaffected by the lack of blinding.
Blinding of outcome assessors	Low risk	Blinding of outcome assessors was done, making it unlikely blinding was lost.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	High risk	Study protocol not available and there was insufficient information to allow judgement.
Other sources of bias	Low risk	The study appeared to have no other sources of bias.

Study characteristics	**Pinheiro et al. (2014)**
Method	Randomized double-blind clinically-controlled study. Allocated 20 participants undergoing bilateral extraction of third molars into 2 groups (n=10) orally administered drug 1 hour before procedure. Group I – *Valeriana officinalis* 100 mg; Group II – placebo.
Participants	20 Participants aged 17-31 years of both genders were selected for bilateral extraction of impacted third lower molars.
Intervention	Two patient groups underwent surgery for extraction of third molars after oral sedation.
Outcomes	Primary outcomes: anxiety, adverse effects (drowsiness, fear and muscle relaxation). Secondary outcomes: vital signs (systolic and diastolic blood pressure, heart rate).
Observations	Pre-operative dose of *Valeriana officinalis* had greater anti-anxiety effect than placebo.

Pinheiro et al. (2014)	**Deemed risk of bias**	**Support for judgement**
Random sequence generation	Low risk	Medications with the same concentrations, size and appearance were placed in envelopes, thus there was sufficient information on the method used for random sequence generation.
Allocation concealment	High risk	Insufficient information on random sequence generation process to allow judgement. It was stated that envelopes were used, but it remained unclear whether these were sealed, opaque or numbered sequentially.
Blinding of participants and personnel	Low risk	Blinding of participants and personnel was done, making it unlikely blinding was lost.
Blinding of outcome assessors	High risk	Insufficient information to judge. The study did not report this information.
Incomplete outcomes	Low risk	There was no loss of outcome data.

Selective outcome reporting	Low risk	The study protocol was available and all pre-specified primary and secondary outcomes of interest in the review were reported as proposed.
Other sources of bias	Low risk	The study appeared to have no other sources of bias.

Study characteristics	**Romano et al. (2011)**
Method	Randomized double-blind clinical trial. Allocated 15 participants undergoing dental implant were orally administered the drug midazolam 15 mg or placebo 1 hour before the procedure. The surgery was carried out by the same operator in 2 surgical visits with 30-day interval between sessions.
Participants	15 participants age 21-50 years of both genders were selected for dental implant placement.
Intervention	Two patient groups underwent surgery for dental implant placement after oral sedation.
Outcomes	Secondary outcomes: vital signs (heart rate).
Observations	No difference for use of 15 mg midazolam versus placebo, with no advantage for incidence of arrhythmias. Anxiolytic premedication failed to prevent arrhythmia.

Romano et al. (2011)	**Deemed risk of bias**	**Support for judgement**
Random sequence generation	High risk	There was insufficient information on procedures for concealing allocation of patients into groups.
Allocation concealment	Low risk	It was stated that envelopes were sealed, providing information on procedures concealing allocation of patients into groups.
Blinding of participants and personnel	Low risk	Blinding of participants and personnel was done, making it unlikely blinding was lost.
Blinding of outcome assessors	High risk	Insufficient information to judge. The study did not report this information.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	Low risk	The study protocol is not available, but the study published clearly included all desired outcomes.
Other sources of bias	High risk	Insufficient information to assess whether there was relevant risk of bias.

Study characteristics	**Silveira-Souto et al. (2014)**
Method	Randomized double-blind crossover clinical study. Allocated 30 participants undergoing surgery for extraction of third

	molars to receive orally administered medication *E. mulungu* 500 mg or placebo, 1 hour before procedure, at first or second surgical intervention, left or right side, compared to placebo group.
Participants	30 participants of both genders were selected for extraction of third molars.
Intervention	Patients underwent surgery for extraction of third molars after oral sedation.
Outcomes	Primary outcomes: anxiety and satisfaction with treatment. Secondary outcomes: vital signs (blood pressure) and oxygen saturation.
Observations	*E. mulungu* can be considered a viable alternative, having produced no meaningful changes in physiological parameters (respiratory depression or motor abnormalities).

Silveira-Souto et al. (2014)	**Deemed risk of bias**	**Support for judgement**
Random sequence generation	Low risk	Randomization was performed using randomized computer-generated numbers, thus there was sufficient information about the method used for generating the random sequence.
Allocation concealment	Low risk	Information was given on procedures for concealing allocation of patients into groups, through coding in protocols
Blinding of participants and personnel	Low risk	Blinding of participants and personnel was done, making it unlikely blinding was lost.
Blinding of outcome assessors	Low risk	Blinding of outcome assessors was done, making it unlikely blinding was lost.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	Low risk	The study protocol is not available, but the study published clearly included all desired outcomes.
Other sources of bias	Low risk	The study appeared to have no other sources of bias.

Study characteristics	**Studer et al. (2012)**
Method	Randomized double-blind crossover study. Allocated 12 participants undergoing surgery for bilateral extraction of third molars to receive drug orally administered 1 hour before procedure. Group I – midazolam 7.5 mg; Group II – clonidine 150 ug. The procedure was performed by the same dental surgeon during two surgical visits with follow-up of 7 days.
Participants	12 participants of both genders were selected for bilateral extraction of third molars.
Intervention	The patients underwent surgery for extraction of third molars after oral sedation.
Outcomes	Primary outcomes: anxiety, adverse effects (dizziness, nausea, headache, fatigue, metallic taste and concentration difficulties. Secondary outcomes: satisfaction with treatment.
Observations	The two medications were rated similar for patient satisfaction. Oral administration of clonidine 150 ug and midazolam 7.5 mg

	medications promoted similar anxiolytic effects before surgery with local anaesthesia.

Studer et al. (2012)	**Deemed risk of bias**	**Support for judgement**
Random sequence generation	Low risk	Randomization was performed using randomized computer-generated list, thus there was sufficient information about the method used for generating the random sequence.
Allocation concealment	High risk	No information or scant description on procedures for concealing allocation of patients into groups.
Blinding of participants and personnel	Low risk	Blinding of participants and personnel was done, making it unlikely blinding was lost.
Blinding of outcome assessors	High risk	The study failed to report this information. Outcomes assessed were subject to influence by the lack of blinding.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	Low risk	The study is not available, but the study published clearly included all the desired outcomes.
Other sources of bias	High risk	Insufficient information to assess whether there was relevant risk of bias.

Characteristics of studies	**Shivananda et al. (2014)**
Method	Randomized double-blind crossover clinical trial. Allocated 20 participants undergoing periodontal surgery. Twenty subjects requiring minimum 2 sextants of flap surgery were selected for the study. Each sextant was randomly assigned into experimental and control sites.
Participants	20 participants of both genders were selected for periodontal surgery, experimental group under 68 kg received diazepam 5 mg and over 68 kg 10 mg - the night before and 1 hour before surgery.
Intervention	Modified widman flap surgery was performed in experimental site with pre-operative oral diazepam sedation and local anaesthesia. Similar surgery was performed in the control site with pre-operative oral placebo and using local anaesthesia only.
Outcomes	Secondary outcomes: oxygen saturation
Observations	There was no statistically significant difference between sedated and non-sedated patients for oxygen saturation. Oral conscious sedation can be used for anxious patients during periodontal surgery for alleviation of anxiety and for better patient acceptance during surgical procedures without significant respiratory depression.

Shivananda et al. (2014)	**Deemed risk of bias**	**Support for judgement**
Random sequence generation	High risk	There was insufficient information on procedure concealing allocation of patients into groups.

Allocation concealment	High risk	No information or scant description on procedures for concealing allocation of patients into groups.
Blinding of participants and personnel	Low risk	Blinding of participants and personnel was done, making it unlikely blinding was lost.
Blinding of outcome assessors	High risk	The study failed to report this information. Outcomes assessed were subject to influence by lack of blinding.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	High risk	The study protocol was not available, thus there was insufficient information to allow judgement.
Other sources of bias	Low risk	The study appeared to have no other sources of bias.

APPENDIX C – LIST OF EXCLUDED STUDIES AND MAIN REASONS FOR EXCLUSION

Other administration route	1. Barclay JK, Hunter KM, Jones H. Diazepam and lorazepam compared as sedatives for out patient third molar surgery. British Journal of Oral Surgery. 1980;18:141-149. 2. Bavisha KA, Elias M, Paris S, Leon AR, Flynn PJ. Comparison of patient-controlled and operator-controlled conscious sedation for restorative dentistry. European Journal of Anaesthesiology. 2004;21:284-288. 3. Cheung CW, Ying CLA, Chiu WK, Wong GTC, Ng KFJ, Irwin MG. A comparison of dexmedetomidine and midazolam for sedation in third molar surgery. Anaesthesia. 2007;62:1132-1138. 4. Fan TWV, Ti LK, Islam I. Comparison of dexmedetomidine and midazolam for conscious sedation in dental surgery monitored by bispectral índex. British Journal of Oral and Maxillofacial Surgery. 2013;51:428-433. 5. Hosie HE, Brook IM, Nimmo WS. Comparison of sedation with temazepam by mouth and diazemuls I.V. for dental surgery. Br J Anaesth. 1988;60:18-23. 6. Luyk NH, Whitley BD. Efficacy of oral midazolam prior to intravenous sedation for there moval of third molars. Int J Oral Maxillofac Surg. 1991;20:264-267. 7. Ochs MW, Tucker MR, White RP, Anderson JA. Recovery following sedation with midazolam or diazepam alone or in combination with fentanyl for out patient surgery. Anesthesia Progress. 1986;230-234. 8. Osborne GA, Rudkin GE, Curtis NJ, Vickers D, Craker AJ. Intra-operative patient-controlled sedation. Anaesthesia. 1991;46:553-556. 9. Rodrigo MRC, Tong CKA. A comparison of patient and anasthetist controlled midazolam sedation for dental surgery. Anaesthesia. 1994;49:241-244. 10. Richmond MN, Daum REO. Premedication with oral slow release morphine in dental anaesthesia: A comparison with temazepam. Anaesthesia. 1988;43:694-696. 11. Stopperich PS, Moore PA, Finder RL, McGirl BE, Weyant RJ. Oral triazolam pretreatment for intravenous sedation. Anesth Prog. 1993;40:117-121.

	12. Rubim J, Schweggmann I, Uys P. Lorazepam as a premedicant in dental surgery. S AfrMed J. 1980;58(3):124-126. 13. Mohamad EM. Midazolam versus but or phanolaslocal an anesthetic adjuncts in oral surgery: a clinical assessment. Egyptian Dental Journal. 1987;33(4):363-374. 14. Zanette G, Manani G, Favero L, Stellini E, Mazzoleni S, Cocilovo F, et al. Conscious sedation with Diazepam and midazolam for dental patient: priority to diazepam. Minerva Stomatol. 2013;62:355-374. 15. Manani G, Baldinelli L, Cordioli G, Consolati E, Luisetto F, Galzigna L. Premedication with Chlordemethyldiazepam and anxiolytic effect of diazepam in implantology. AnesthProg. 1995;42:107-112. 16. Lieblich SE, Horswell B. Attenuation of anxiety in ambulatory oral surgery patients with oral triazolam. J Oral Maxillofac Surg. 1991;49:792-795. 17. Luyk NH, Weaver JM, Beck FM, Loetscher CA, Sacks J. The effectiveness of flurazepam as night sedation prior to there moval of third molars. Int J Oral Maxillofac Surg. 1988;17:347-351. **18.** O'Boyle CA, et al. Comparison of midazolam by mouth and diazepam I.V. in out patient oral surgery. Br J Anaesth. 1987;59:746.
Not oral surgery	19. Ahmed N, Khan FA. Evaluation of oral midazolam as pre-medication in day care surgery in adult Pakistani patients. J Pak Med Assoc. 1995;45(9):239-241. 20. Hargreaves J. Benzodiazepine premedication in minorday-case surgery: comparison of oral midazolam and temazepam with placebo. Br J Anaesth. 1988; 61:611-616. 21. Patel T, Kurdi MS. A comparative study between oral melatonin and oral midazolam on preoperative anxiety, cognitive, and psychomotor functions. Journal of Anaesthesiology Clinical Pharmacology. 2015;31(1):37-43. 22. Baird ES, Curson I. Orally administered diazepam in conservative dentistry. British Dental Journal. 1970;128:25-27. 23. Irjala J, Kanto J, Irjala K, Salonen M, Viinamaki O. Temazepam versus flunitrazepam as na oral premedication in adult surgical patients. European Journal of Anesthesiology. 1987;4:435-440. 24. Raybould D, Bradshaw EG. Premedication for day case surgery: a study of oral midazolam. Anaesthesia. 1987;42:591.
Not RCT (n=12)	25. Johren P, Jackowski J, Gangler P, Sartory G, Thom A. Fear reduction in patients with dental treatment phobia. British Journal of Oral and Maxillofacial Surgery. 2000;38:612-616. 26. Ochs MW, Tucker MR, White RP. A comparison of amnesia in outpatients sedated with midazolam or diazepam alone or in combination with fentanyl during oral surgery. JADA. 1986;113:894-897. 27. Khosla VM, Boren W. Diazepam (Valium) as preoperative medication in oral surgery. Anesthesiology. 1969;28(5):671-679. 28. Debernardi G, Debernardi C. Sperimentazione clinicasull'azione di una benzodiazepine (Lexotan) sulcomportamento del paziente ansiosonell'ambulatorio odonto stomatologico. Min Stom. 1985; 34:323-328. 29. Noguchi T, Hayano Y, Iwasaka H, Miyamoto M, Habu A, Tsuzaki K, et al. A study of clinical efficacy of triazolam as preanesthetic medication. 1985;34(4):493-499. 30. Shane SM, Baltimore. Amnesia for brief exodontia procedures using small doses of diazepam and methohexital with local block anesthesia for ambulatory patients. J Oral Surgery. 1971;29:191-193. 31. Skelly AM, Boscoe MJ, Dawling S, Adams AP. A comparison of diazepam and midazolam as sedatives for minor oral surgery. European Journal of Anaesthesiology. 1984;(1):253-267.

	32. Wahlmann UW, Dietrich U, Fischer W. Zurfrage der oral em sedierung mit midazolam bei ambulante zahnarztlich-chirurgischen eingriffen. Disch Zahnarztl Z. 1992;47:66-68. 33. Reinhardt LC, Felberg RV, Lemes CHJ. Comparative study of bone response guided tissue regeneration clinical evaluation of the anxiety and cardiovascular parameters with the use of anxiolitic in the pre-operative in bucomaxilofacial surgery. Full Dentistry in Science. 2010;1(4):328-331. 34. Aeschliman SD, Blue MS, Williams KB, Cobb CM, MacNeill SR. A preliminary study on oxygen saturation levels of patients during periodontal surgery with and without oral conscious sedation using diazepam. J Periodontol. 2003;74(7):1056-1059. 35. Moorthi RK, Kumar MPS. Pre- and post-operative anxiety in patients undergoing dental extractions. Drug Ivention Today. 2018;10(12):2445-2449. 36. James D, Nazar N. Role of anti- anxiety drugs patient cooperation during minor surgical procedure. Research J. Pharm. and Tech.2018; 11(8): 3389-3391
Other medication or comparator	37. Kanto D, Salo M, Happonen RP, Vahlberg T, Kanto J. Tramadol premedication in operative extraction of the mandibular third molar: a placebo-controlled crossover study. Acta Odontologica Scandinavica. 2005; 63:43-49. 38. White CS, Dolwick MF, Gravenstein N, Paulus DA. Incidence of oxygen desaturation during oral surgery out patient procedures. J Oral Maxillofac Surg. 1989;47:147-149. 39. Dellovo AG, Souza LMA, Oliveira JS, Amorim KS, Groppo FC. Effects of auriculotherapy and midazolam for anxiety control in patients submitted to third molar extraction. Int J Oral Maxillofac Surg. 2018;18:1-6.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5,6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5, 6 and 17
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7, 8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7, 8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8 to 10 and Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10 to 13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8 to 10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13 to 15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15, 16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16, 17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

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EFFECTIVENESS AND SAFETY OF ORAL SEDATION IN ADULT PATIENTS UNDERGOING DENTAL PROCEDURES: A SYSTEMATIC REVIEW

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EFFECTIVENESS AND SAFETY OF ORAL SEDATION IN ADULT PATIENTS UNDERGOING DENTAL PROCEDURES: A SYSTEMATIC REVIEW

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ABSTRACT

Objectives: It can be challenging to manage patients who are anxious during dental procedures. There is a lack of evidence regarding the effectiveness and safety of oral sedation in adults. This study evaluated the effectiveness and safety of oral sedation in patients undergoing dental procedures.

Design: Systematic Review

Methods: Randomized clinical trials (RCTs) that compared the oral use of benzodiazepines and other medications versus a placebo or other oral agents in adult patients. A search of the Cochrane (CENTRAL), MEDLINE (via Ovid), EMBASE (via Ovid), and CINAHL (via Ovid) databases was conducted, without any restrictions on language or date of publication. The primary outcomes included the adverse effects and anxiety level. The secondary outcomes included sedation, satisfaction with the treatment, heart rate, respiratory rate, blood pressure, and oxygen saturation. Reviewers, independently and in pairs, assessed each citation for eligibility, performed the data extraction, and assessed the risk of bias. A narrative synthesis of the data was provided.

Results: A number of RCTs (n=327 patients) assessed the use of benzodiazepines (n=9) and herbal medicines (n=3). We found good satisfaction with treatment after the use of midazolam 7.5 mg or clonidine 150 µg and reduced anxiety with alprazolam (0.5 and 0.75 mg). Midazolam 15 mg promoted greater anxiety reduction than *Passiflora incarnata* L 260 mg, while *Valeriana officinalis* 100 mg and *Erythrina mulungu* 500 mg were more effective than a placebo. More patients reported adverse effects with midazolam 15 mg. Diazepam 15 mg and *V. officinalis* 100 mg promoted less change in the heart rate and blood pressure than a placebo.

Conclusions: Given the limitations of the findings due to the quality of the included studies and the different comparisons made between interventions, further RCTs are required to confirm the effectiveness and safety of oral sedation in dentistry.

Protocol registration: PROSPERO CRD42017057142.

Strengths and limitations of this study

- We performed a comprehensive systematic review to identify randomized clinical trials that evaluated the effectiveness and safety of oral sedation in patients undergoing dental surgical procedures.
- Anxiety can lead to dental treatment avoidance with consequent exacerbation of poor oral health in phobic patients; therefore, it is important to understand which drugs are effective for anxiety control, as this can contribute to patient compliance to dental treatment.
- Adverse effects from oral sedatives are negative outcomes in dentistry that should be avoided; therefore, it is important that we estimate the risk of such effects so that decision-making regarding conscious sedation can be better informed.
- This study was carried out with methodological rigor, including explicit eligibility criteria, a broad extensive database search, study selection by reviewers working in pairs and independently, and evaluation of the risk of bias.
- The quality of the included studies and different comparisons made between interventions were limiting factors for the study findings.

INTRODUCTION

Anxiety during dental treatment can cause stress and discomfort in patients and lead to dental treatment avoidance with consequent damage to the oral health of phobic patients.[**1,2]** In this context, effective control of anxiety plays a pivotal role in patient compliance to dental treatment. The use of conscious sedation is an important strategy for the behavioral management of patients who suffer from anxiety over dental treatment.**[3]** Conscious sedation is an approach that uses one or more drugs to produce a state of central nervous system depression while maintaining verbal contact with the patient throughout the procedure.[4] The sedation level should be such that the patient remains conscious and can readily understand and respond to verbal instructions or tactile stimulation.[5]

Indications for the use of conscious sedation include a diagnosis of anxiety and dental phobia, prolonged or traumatic dental procedures, and medical conditions potentially aggravated by stress, which can reduce the patient's ability to cooperate.[6]

Additionally, the release of endogenous catecholamines can increase the cardiovascular system load in patients with a history of angina, whereas asthmatic patients can present stress-induced acute episodes of breathing difficulty induced by stress. These are among some of the patients' profiles that can benefit from conscious sedation in reducing exacerbation risk. The risk-benefit should be determined according to the severity of the patient's condition.[7]

Oral sedation is one of the relatively accessible means for dental professionals to control patient anxiety. However, oral sedation can have inherent limitations due to the pharmacokinetics of the orally administered drug, such as delayed and variable onsets of action.[8] Moreover, drug interventions to provide conscious sedation should have a sufficient safety margin to preclude consciousness loss.[9]

Benzodiazepines are widely used in oral sedation to induce a state of anxiety in dental procedures.[10] These drugs are among the most commonly prescribed and employed for this purpose worldwide.[5, 8, 11, 12]

Although benzodiazepines have a similar mechanism of action, their pharmacokinetics differ, which are key factors in selecting the best option to suit the patient.[13] The different oral sedation options in dentistry include midazolam, diazepam, and lorazepam as mainstream drugs, although alprazolam, temazepam, and oxazepam have also been used.[8]

Few studies have synthesized the available evidence on the effectiveness and safety of oral sedation in adults undergoing dental procedures. A systematic review evaluated the safety of using drugs for sedation administered by oral, intranasal, sublingual, intramuscular, and intravenous routes in adults undergoing dental procedures. However, the data extraction was not performed in pairs and independently, and the risk of bias or quality of the evidence was not assessed.[10] Another systematic review investigated the use of midazolam in dental surgical procedures. Of the ten studies included in the review, only three addressed oral use, while the other studies combined drugs administered orally and via other routes.[14]

The hypothesis of this study was that conscious oral sedation is effective and safe for use in dental procedures. The gap in knowledge on the use of drugs for oral sedation in dentistry prompted this systematic review to determine the effectiveness and safety of oral sedation drugs in adult patients undergoing dental surgical procedures.

METHODS

Protocol registration

The protocol of this systematic review was registered on the PROSPERO – *International Prospective Register of Systematic Reviews* (registration number CRD42017057142) at the site address: (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=57142) and also published.[15]

The population, intervention comparator, and outcomes (PICO) strategy used was as follows: *population:* adults requiring dental surgical procedures; *intervention:* oral sedation; *comparator:* placebo group or other oral drug administered; *outcomes:* effectiveness: anxiety, sedation, and satisfaction with the treatment; and safety: adverse effect, heart rate, respiratory rate, blood pressure, and oxygen saturation.

Patient and Public Involvement

No patients were involved.

Eligibility criteria of the studies

Inclusion criteria

Participants: Adults requiring dental surgical procedures, such as dental extraction, surgery for orthodontic purposes, removal of residual roots and third molars, dental implants, and other dental surgical interventions.

Intervention: At least one group used oral sedation with benzodiazepines or other drugs (e.g., herbal medicines).

Comparator: Placebo group or other drug administered orally.

Study: Randomized clinical trials (RCTs).

Exclusion criteria

Studies involving adults with respiratory diseases, with contraindications to benzodiazepine, pregnant and/or breastfeeding women, and those with a history of allergies were not included. Studies that combined the administration of different drugs for oral sedation were also excluded.

Outcomes assessed

Primary outcomes

1) Effectiveness was measured by improvement in anxiety by using the Dental Anxiety Scale (DAS), Oral Surgery Confidence Questionnaire (OSCQ), and/or other scales for anxiety symptoms.

2) Safety was measured by the number of participants that reported side effects, number of adverse effects (or adverse drug reactions), and number of participants that dropped out due to side effects.

Secondary outcomes

1) Secondary outcomes of effectiveness were sedation and satisfaction with the treatment.

2) Secondary outcomes of safety were heart rate, respiratory rate, blood pressure, and oxygen saturation.

Search method for identifying studies

Electronic database search

The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL), which includes Dentistry and Oral Health Group's Specialized

Register; MEDLINE (via Ovid); Excerpta Medica Database (EMBASE) (via Ovid); Cumulative Index to Nursing and Allied Health Literature (CINAHL) (via Ovid), Lilacs (Scielo), and the Capes database (https://catalogodeteses.capes.gov.br/catalogo-teses/#!/), without restrictions on language or publication date, with the search encompassing articles published between inception and March 12, 2020.

Other reference search sources

The reviewers (CCB and JOA) manually analyzed the reference list or citations of the articles to retrieve and identify other possible eligible studies. The main authors and/or pharmaceutical companies involved in producing the drugs were contacted for information on additional trials, if necessary.

Search strategy

The search was conducted using Medical Subject Headings terms for each oral surgical procedure (such as oral surgery, dental extraction, and dental implant), benzodiazepines (and its synonyms), and terms to search for other drugs. The search strategy for MEDLINE (via Ovid) was adapted for each database (Appendix A).

Study records

Data management

After performing the search strategies on each electronic database, the researchers imported the results from each search into an EndNote library. Duplicate entries were identified and removed.

Study eligibility determination

Relevant data from the eligible studies were independently extracted into Microsoft Excel, using a standardized data extraction form. Four reviewers (JDOA and CCB, CCG, and NKA), working in pairs and independently, selected potentially relevant titles and abstracts and applied the eligibility criteria. Full texts of the potentially eligible articles were obtained. Similarly, the reviewers checked the eligibility of each study. Disagreements were resolved by consensus and when necessary, arbitrated by a third reviewer (RHLM or LCL).

Data extraction

The same reviewers (JDOA and CCB, CCG, and NKA), working in pairs and independently, used a standardized and pretested form for data extraction. Subsequently, the reviewers extracted the patient data, methods, interventions, and outcomes. We contacted the authors for articles with incomplete methods and results data, if necessary. Disagreements were resolved by consensus and when necessary, arbitrated by a third reviewer (RHLM or LCL).

Risk of bias

A modified version of the Cochrane collaboration approach for assessing the risk of bias was used.[16,17] The same reviewers, again in pairs and independently, evaluated the risk of bias for each clinical trial according to randomization; allocation concealment; blinding of patients, health professionals, and outcome assessors; incomplete outcome data; selective outcome reporting and major baseline imbalance characterizing the sample.

The same reviewers attributed the standard answers "definitely yes," “probably yes,” “probably no,” and “definitely no” for each domain; with “definitely yes” and

"probably yes" denoting a low risk of bias and "definitely no" and "probably no" attributing a high risk of bias.[18] Similarly, the reviewers resolved disagreements by consensus. Disagreements were resolved by consensus and, when necessary, arbitrated by a third reviewer (RHLM or LCL).

Data synthesis and analysis of the quality of evidence

A narrative synthesis of the findings was carried out. The extracted data were summarized in the tables with the measures (mean, standard deviation, absolute and relative frequency).

Heterogeneity were explained by drug doses (higher vs lower) with greater effect than expected at higher doses and treatment time (longer vs shorter).[15] Due to the divergences between the drugs prescribed and the doses used and measured outcomes, a meta-analysis was not performed, and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) could not be produced.[19, 20]

RESULTS

Search strategy results

A total of 3,669 publications were retrieved, of which 49 were included for full-text selection. After application of the eligibility criteria, 10 RCTs were included in the review (Figure 1). The studies' characteristics are given in Appendix B, and the excluded studies are listed in Appendix C.

Description of the studies included

The 10 RCTs involved 327 patients (58% females) undergoing oral surgery. Most of the RCTs evaluated the use of benzodiazepines (n=9), and three studies assessed the

use of herbal medicines for oral sedation. The majority of the studies were conducted by Brazilian researchers between 2011 and 2017. Only one study was funded by the pharmaceutical industry (Table 1).

Table 1. Characteristics of the studies included (n=10 studies)

Variables	Studies (n)	Population (n)
Study population	10	327
Females (n=282)	8	164 (58.2%)
BENZODIAZEPINES		
Alprazolam (0.25, 0.5 and 0.75 mg)	1	36
Diazepam (5, 10 e 15 mg)	3	49
Midazolam (7.5 and 15 mg)	4	97
Lorazepam (1 mg)	1	10
HERBAL MEDICINES		
Erythrina mulungu 500 mg	1	30
Passiflora incarnata L. 260 mg	1	40
Valeriana officinalis 100 mg	1	10
CLINICAL CONDITION		
Dental extraction	6	180
Dental implants	2	45
Other dental surgery	2	102
COUNTRY		
Brazil	5	135
United States of America	1	48
Italy	1	82
Switzerland	1	12
China	1	30
India	1	20
YEAR OF PUBLICATION		
1979-1988	2	112
1989-1998	1	48
1999-2008	0	0
2009-2017	7	167
FUNDED BY INDUSTRY		
Yes	1	30
Not specified	4	157
Not funded	5	140

Risk of bias (Figure 2)

Random sequence generation

Some studies failed to report sufficient data on the randomization process, precluding any assessment, and exhibited selection bias.[21-27] Some stated that patients were randomly allocated to groups but did not detail the process used.

Allocation concealment

Some studies guaranteed that the random sequence generation of participants was unpredictable since the envelopes handed to participants were sealed and coded.[22, 24, 28] By contrast, other clinical trials did not guarantee allocation concealment.[21, 23, 25, 27, 29] Two clinical trials provided insufficient information on the random sequence generation process employed.[26, 30]

Blinding of the participants and personnel

Rodrigo, Cheung [22], and Coldwell et al. [23] clearly described that the blinding of participants and personnel was ensured and unlikely to have been lost and had no performance bias. The remaining studies stated that they were double-blind but provided no further details.[21, 24-30] Consequently, these studies were deemed "probably yes" and considered as having a low risk of bias.

Blinding of the outcome assessors

Blinding of the outcome assessors was performed in three studies, making it unlikely that blinding was lost.[22, 27, 28] Romano et al.[24] and Pinheiro et al.[30] stated that the professionals were blinded, but it was unclear whether they were blinded to the outcome collection. The other studies did not report this information, indicating detection bias.[21, 23, 25, 26, 29]

Incomplete outcomes

For the study by Coldwell et al.,[23] it was impossible to judge whether incomplete outcome reporting occurred. The remaining studies reported whether any participants were lost to follow-up or excluded for another reason.

Selective outcome reporting

One RCT recorded their protocol allowing confirmation that there was no selective outcome reporting.[30] Although the study protocol was not reported for the other studies, it appears that they reported all the desired outcomes.

Other sources of bias

Only one study cited the source of funding.[22] Other studies declared there was no funding.[21, 22, 25-28, 30] The remaining studies did not report sufficient information to assess the presence of other sources of bias.[23, 24, 29]

Outcomes assessed

The primary and secondary outcomes reported by the studies are described in Tables 2, 3, and 4.

309 **Table 2. Primary and secondary outcomes reported by the studies (n= 9)**

AUTHOR/YEAR (n= participants)	INTERVENTION GROUP (n= participants)	COMPARATOR GROUP (n= participants)	*PRIMARY OUTCOMES (scales)	PRIMARY OUTCOME RESULTS	SECONDARY OUTCOMES	SECONDARY OUTCOME RESULTS
Coldwell et al. (1997)[23] (n=48)	Alprazolam 0.25 mg (n=12) Alprazolam 0.5 mg (n=12) Alprazolam 0.75 mg (n=12)	Placebo (n=12)	Anxiety *(DAS, OSCQ and ISAR)*	Decrease in number of anxious patients with increasing doses of alprazolam	Not reported	
Branco, Bassualdo (2012)[25] (n=30)	Diazepam 10 mg (n=10) Lorazepam 1 mg (n=10)	Placebo (n=10)	Anxiety *(Corah's DAS)*	Decreased anxiety compared to baseline levels, but no statistical difference between groups	Not reported	
Studer et al. (2012)[29] **Crossover** (washout of 30 days) (n=12)	Midazolam 7.5 mg (n=12)	Clonidine 150 ug (n= 12)	Not reported		Satisfaction with the treatment Blood pressure (BP)	77% of patients (midazolam group) vs 75% (clonidine group) No statistical difference between the groups for BP
Silveira-Souto et al. (2014)[28] **Crossover** (washout of 15 days) (n=30)	*Erythrina Mulungu* 500 mg (n=30)	Placebo (n=30)	Anxiety *(Corah's DAS)*	Decreased anxiety compared to baseline levels, but no statistical difference between groups	Heart rate Blood pressure Oxygen saturation	No statistical difference between the groups for outcomes

Dantas et al. (2017)[27] **Crossover (**washout of 15 to 30 days) (n=40)	*Passiflora incarnata L.* 260 mg (n=40)	Midazolam 15 mg (n=40)	Anxiety *(Corah's DAS)*	Decreased anxiety compared to baseline levels, but no statistical difference between groups	Heart rate Blood pressure Oxygen saturation	No statistical difference between the groups for outcomes
Pinheiro et al. (2014) (n=20)[30]	*Valeriana officinalis* 100 mg (n=10)	Placebo (n=10)	Anxiety *(DAS)*	Herbal medicine was more effective than placebo	Heart rate Blood pressure	No statistical difference between the groups for outcomes
Romano et al. (2011) (n=40)[24]	Midazolam 15 mg (n=20)	Placebo (n=20)	Not reported		Heart rate	No statistical difference between the groups
Manani et al. (1979) [21] (n=82)	Diazepam 15 mg (n=19) Trazodone 25 mg (n=20) Trazodone 50 mg (n=21)	Placebo (n=22)	Not reported		Heart rate Blood pressure	No statistical difference between the groups
Shivananda et al. (2014)[26] **Crossover** (n=20) **(**washout: not reported)	Diazepam 5 mg (n=20) Diazepam 10 mg (n=20)	Placebo (n=20)	Not reported		Oxygen saturation	No statistical difference between the groups

*The primary outcome “adverse effect” is reported in Tables 3 and 4.
Dental Anxiety Scale (DAS): categorizes participants into not anxious, slightly anxious, fairly anxious, and very anxious.
Oral Surgery Confidence Questionnaire (OSCQ): contains 11 items rated from 0: not at all confident to 9: extremely confident).
Interval Scale of Anxiety Response (ISAR): contains a 90 mm vertical line labeled with descriptors alongside intervals determined according to estimated magnitude: “calm, relaxed,” “a little nervous,” “tense, upset,” “afraid,” “very afraid,” “panicked” and “frightened”;
Corah's Dental Anxiety Scale: contains four questions with five possible answers that assess the patient's feelings, reactions, and reactions related to the dental procedure, as: very little anxious (up to five points), slightly anxious (6-10 points), moderately anxious (11-15 points) points and extremely anxious (16-20 points).
Visual Analog Scale (VAS): ratings range from "no satisfaction" (0%) and "complete satisfaction" (100%).

Due to differences between drugs used across groups, a meta-analysis of the data could not be performed, and the results were expressed in the form of a narrative synthesis. None of the studies reported sedation outcomes and respiratory rates.

Of the primary outcomes, five studies reported the anxiety levels,[23, 25, 27, 28, 30] and six studies collected information on the adverse effects.[21-23, 27, 29, 30]

Table 3 describes the studies that report the percentage of participants who experienced adverse effects. In general, most participants exhibited some adverse effects. Dantas et al.[27] reported the number of adverse effects but did not report the number of patients with adverse effects. Coldwell et al.[23] did not specify the adverse effect by group. Therefore, we did not include their results in the table.

Table 3. Description of studies that reported the number of participants that experienced adverse effects and dropped out due to adverse effects (n= 4)

Authors (year)	Groups	N. of participants with adverse effects/total (%)	N. of participants that dropped out
Studer et al. (2012)[29]	Midazolam 7.5 mg	6/12 (50.0)	0
	Clonidine 150 ug	5/12 (41.6)	
Rodrigo & Cheung (1987)[22]	Midazolam 15 mg	17/30 (56.6)	0
	Placebo	9/30 (30.0)	
Manani et al. (1979)[21]	Trazodone 25 mg	12/20 (60.0)	0
	Trazodone 50 mg	11/21 (52.3)	
Pinheiro et al. (2014)[30]	*Valeriana officinalis* 100 mg	9/10 (90.0)	0
	Placebo	7/10 (70.0)	

The number of reports of adverse effects is shown in Table 4. In general, a higher number of adverse effects was associated with the use of midazolam compared to *P. incarnata* and a placebo, where the most reported adverse effects were drowsiness, muscular relaxation, and dizziness.[22, 27]

330 **Table 4 - Description of the adverse effects reported by the included studies (n= 5)**

Author/year	Intervention group (number of AE)	Description of the effects (number of AE)	Comparator group (number of AE)	Description of the effects (number of AE)
Dantas et al. (2017)[27]	Midazolam 15 mg (54)	Drowsiness (33), muscular relaxation (11), dizziness (7), gastrointestinal problems (1), amnesia (1) insomnia (1)	*Passiflora incarnate* (32)	Drowsiness (20), muscular relaxation (8), dizziness (2), allergy (1), epistaxis (1)
Manani et al. (1979)[21]	Diazepam 15 mg (36)	Drowsiness (10), vertigo (3) cognitive impairment (6)	Trazodone 50 mg (28)	Drowsiness (10), vertigo (5), blurred vision (2) cognitive impairment (11)
			Trazodone 25 mg (18)	Drowsiness (15), vertigo (9), blurred vision (6) cognitive impairment (6)
			Placebo (18)	Drowsiness (12), vertigo (1), blurred vision (2) cognitive impairment (3)
Pinheiro et al. (2014)[30]	*Valeriana officinalis* (16)	Drowsiness (9) muscular relaxation (7)	Placebo (11)	Drowsiness (7) muscular relaxation (4)
Rodrigo; Cheung (1987)[22]	Midazolam 15 mg (46)	Drowsiness (17), dizziness (8), memory loss (3), excitability(5), depression (5), nausea (5), vomiting (2), headache (3)	Placebo (29)	Drowsiness (9), dizziness (4), memory loss, excitability (1), depression (1), blurred vision (1), insomnia (5), hallucinations (1), nausea (4), vomiting (1), headache (2)
Studer et al. (2012)[29]	Midazolam 7.5 mg (6)	Dizziness (3), nausea, headache, and fatigue (1) cognitive deficit (2)	Clonidine 0.15 mg (6)	Nausea (2), drowsiness (3) fainting (1)

331 AE: adverse effects

332

The secondary outcomes reported were patient satisfaction with treatment (n= 1 study),[29] heart rate (n= 5 studies),[21, 24, 27, 28, 30] blood pressure (n= 5) [21, 27-29, 30], and oxygen saturation (n= 3).[26, 28]

Reporting of the outcomes by drug

Alprazolam (0.25, 0.5 and 0.75 mg)

In a placebo-controlled RCT, 48 participants undergoing dental extraction were allocated into four groups (n= 12 per group): group I: alprazolam 0.25 mg; group II: alprazolam 0.50 mg; group III: alprazolam 0.75 mg; and group IV: placebo. Anxiety was assessed using the DAS, OSCQ, and the Interval Scale of Anxiety Response (ISAR). The proportion of individuals that reported feeling fairly to very anxious during oral surgery decreased with increased doses of alprazolam. The most commonly observed adverse effect associated with the use of alprazolam at doses of 0.25 mg, 0.50 mg, and 0.75 mg was anterograde amnesia.[23]

Diazepam (5, 10, and 15 mg) and lorazepam (1 mg)

In a double-blind and placebo-controlled RCT, 30 participants undergoing dental implant placement surgery were allocated into three groups (n= 10 per group). One hour before the procedure, they received the following interventions: group I: diazepam 10 mg; group II: lorazepam 1 mg; and group III: placebo. Anxiety was measured based on the Corah DAS. No significant difference was found between the groups concerning this outcome.[25]

An RCT allocated 82 patients undergoing outpatient dental surgery to group I: placebo, group II: trazodone 25 mg, group III: trazodone 50 mg, and group IV: diazepam 15 mg. A comparison of the reported adverse effects for trazodone versus diazepam

revealed that diazepam was associated with more effects. The main effects reported were drowsiness, vertigo, and cognitive impairment. In addition, the number of individuals in use of diazepam reporting adverse effects was also higher. No difference in the heart rate and blood pressure were observed between the groups.[21]

An RCT with a crossover design (washout not reported) allocated 20 participants undergoing periodontal surgery to group I: diazepam 5 mg or 10 mg (according to body weight) or group II: placebo, 1 h before surgery. No significant differences in oxygen saturation were observed between the groups.[26]

Midazolam (7.5 and 15 mg)

An RCT with a crossover design (washout of 30 days) allocated 12 patients undergoing bilateral surgical third molar extraction to receive the following interventions 1 h before the procedure: group I, midazolam 7.5 mg and group II, clonidine 150 µg. The level of satisfaction with the treatment was determined using the visual analog scale (VAS) with ratings ranging from "no satisfaction" (0%) to "complete satisfaction" (100%). Around 77% of the patients who received midazolam were satisfied compared to 75% of those given clonidine. There was no difference in the number of participants or adverse effects. No significant difference was observed in heart rate between the groups studied.[29]

Another RCT allocated 15 participants undergoing implant placement to receive either group I: midazolam 15 mg or group 2: placebo 1 h before the procedure. The use of midazolam proved ineffective as a premedication anxiolytic for preventing myocardial arrhythmias.[24]

A RCT with a crossover design allocated 30 patients undergoing bilateral surgical third molar extraction to group I: midazolam 15 mg (single dose) or group II: placebo 45

min before the dental procedure. They reported a higher number of adverse effects with midazolam compared to placebo, in particular drowsiness, dizziness, and excitability.[22]

***Erythrina mulungu* 500 mg**

The effectiveness of *E. mulungu* 500 mg (single dose) was assessed in a crossover design RCT (washout period of 15 days) involving 30 patients undergoing bilateral extraction of impacted third molars compared to placebo. Both drugs were administered 1 h before the dental procedure. Anxiety was determined based on the Corah DAS scores. Volunteers with higher anxiety levels tended to prefer herbal medicine. The heart rate, systolic and diastolic blood pressure, and oxygen saturation were not significantly different between the groups studied.[28]

***Passiflora incarnata* L. 260 mg and midazolam 15 mg**

An RCT with a crossover design allocated 40 participants undergoing mandibular third molar extraction into two groups (washout period of 15–30 days). Each group received interventions 30 min before the procedure: group I, 260 mg of *P. incarnata* and midazolam 15 mg. The Corah DAS was used before and after the surgical procedure. Both drugs proved to be effective for controlling anxiety, although midazolam 15 mg was more effective than herbal medicine. The most frequent adverse effects, particularly drowsiness, and muscular relaxation, occurred with midazolam. The heart rate, systolic and diastolic blood pressure, and oxygen saturation were not significantly different between the groups.[27]

***Valeriana officinalis* 100 mg**

A crossover RCT (washout period of 15 days) allocated 20 participants undergoing bilateral third molar extraction into two groups that received the intervention 1 h before the procedure: group I: *V. officinalis* 100 mg and group II: placebo. Anxiety was measured using the DAS. Herbal medicine was more effective in controlling anxiety than a placebo. No differences were reported in the number of adverse effects, with the most common being drowsiness and muscular relaxation. Herbal medicine promoted less change in the heart rate and blood pressure compared to a placebo.[30]

DISCUSSION

Main findings and literature comparison

This review has evaluated the available evidence on the effectiveness and safety of oral sedation in adults undergoing dental procedures using 10 RCTs. The majority of the RCTs evaluated benzodiazepine class drugs for oral sedation, where the most commonly used was midazolam. Most of the studies were conducted in Brazil, none of which met all the evaluation criteria for risk of bias. The main methodological flaws were related to randomization and allocation concealment.

The heterogeneity of the interventions and doses precluded a meta-analysis for all the outcomes assessed being performed. The primary outcomes reported by the studies were anxiety and the adverse effects.[21-23, 25, 27-30]

In general, alprazolam (0.5 and 0.75 mg),[23] midazolam 15 mg, *P. incarnata* 260 mg,[27] *V. officinalis*,[30] and *E. mulungu*,[28] were considered effective for controlling anxiety.

The results revealed a higher number of adverse effects associated with midazolam use,[22, 27] followed by diazepam.[21] In addition, a greater number of

patients reported adverse effects from these benzodiazepines. However, these findings should be interpreted with caution, given that the high number of reports might be related to the larger number of participants in these studies. Moreover, these findings are based on reports of only one study, where a lack of comparability between studies hampers any meaningful conclusion.

There was no difference in the number of patients that exhibited adverse effects after using midazolam 7.5 mg and clonidine 150 ug,[29] but more adverse effects were reported in the group that received midazolam 15 mg than in the placebo group. These results suggest that an increase in midazolam dose may be associated with a higher number of adverse effects.

No difference was found between midazolam 7.5 mg and clonidine 150 µg regarding satisfaction with the treatment.[29] The physiological parameters showed no statistical difference by any intervention. No significant differences in the heart rate or blood pressure were evident when comparing *E. mulungu* to placebo,[28] *P. incarnata* to midazolam,[27] midazolam to clonidine,[29] diazepam to placebo, or trazodone.[21] However, the use of *V. officinalis* was associated with less change in these parameters relative to a placebo.[30] There was no difference in oxygen saturation for the use of *E. mulungu* versus placebo,[28] *P. incarnata* versus midazolam,[27] or diazepam versus placebo.[26]

Although there are public policies aimed at herbal medicines in Brazil, such as the National Program for Medicinal Plants and Herbal Medicines (Decree No. 5,813 of 2006); the use of herbal medicines is not common in dentistry. Three RCTs with herbal medicines were from Brazil, this is probably because oral sedation is a common practice in dental procedures compared to other countries that use intravenous and other routes for sedation.

Previous systematic reviews could not be compared with the present study's findings because the RCTs included in these reviews were not restricted to the oral route.[10, 14] Also, these reviews failed to report most of the outcomes assessed in the present study.

A previous systematic review assessed the safety of using sedation drugs by any administration route in patients undergoing dental procedures. Ten of the studies included were RCTs, but none of these were included in our study because they used a combination of drugs or other routes of administration. Midazolam was the most commonly used drug, irrespective of the administration route. Although the authors stated that the drug appeared to be safe for sedation, the risk of bias of the studies was not considered, and further clinical trials were suggested to confirm the findings.[10]

Another systematic review investigated the anxiolytic effect of midazolam in dental surgery, regardless of the administration route.[14] Of the ten studies reviewed, three involved oral administration, of which only one RCT was included in the present study since the other clinical trials used a combination of different drugs or alternative routes of administration.[29]

In the literature, no secondary studies that compared outcomes with the treatment and physiological parameters were found.

Study strengths and limitations

This review was carried out with methodological rigor and evaluated the risk of bias., which has not been performed previously in similar reviews.[10, 14] The strengths of the present review include its explicit eligibility criteria, broad extensive database search, and study selection by reviewers working both independently and in pairs.

The primary studies included are a limiting factor to the findings due to their methodological quality, the non-reporting of clinical outcomes, and different comparator groups. This meant that a meta-analysis could not be conducted. Another notable factor was the heterogeneous method of reporting anxiety outcomes among studies.

It is also noteworthy that the vast majority of the RCTs (90%) failed to consider the patient´s anxiety level as a study inclusion criterion. Only one study reported that patients with higher anxiety levels tended to prefer herbal medicine.[28] This information is important in that according to the literature, oral sedation can help most patients with mild to moderate levels of fear and anxiety but may be ineffective in patients with high levels of anxiety.[11, 31]

Implications for clinical practice and research

Our findings suggest that benzodiazepines and herbal-based medicines could be safely used for oral sedation in outpatient dental surgical procedures. Dental surgeons should devise surgical plans based on the patient's condition. This requires a detailed analysis in which the patient´s level of anxiety and fear concerning the procedure is determined so that the most suitable medication can be administered.

None of the RCTs evaluated all of the outcomes proposed to determine the effectiveness and safety of oral sedation in dental surgical procedures. Also, a comparison between the studies was not possible due to the different drugs investigated. Therefore, further clinical trials adopting more methodological rigorous data collection and methodological guidelines should be conducted.

It is important to point out that although the findings of this review are somewhat limited, benzodiazepines and herbal-based medicines both appear to be safe under the conditions reported in the RCTs included (single dose administered orally).

The present review synthesizes the available evidence on the effectiveness and safety of oral sedation in adults undergoing dental surgical procedures. This can help guide the decision-making process in dental practice so as to reduce patient anxiety in clinical procedures.

CONCLUSION

The results suggest that the use of alprazolam, midazolam, *P. incarnate, V. officinalis,* and *E. mulungu* is effective and safe in controlling anxiety among adult patients undergoing dental interventions. Midazolam was the most studied drug and was associated with the highest rate of adverse effects. However, given the study's limitations concerning the number of studies reviewed, different comparisons between the studies, and incomplete outcome reporting, further clinical trials should be conducted to confirm the effectiveness and safety of these drugs.

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FIGURE LEGENDS

Figure 1 – Flow chart of study selection process

Figure 2 – Consensus of authors

Figure 1 – Flow chart of study selection process

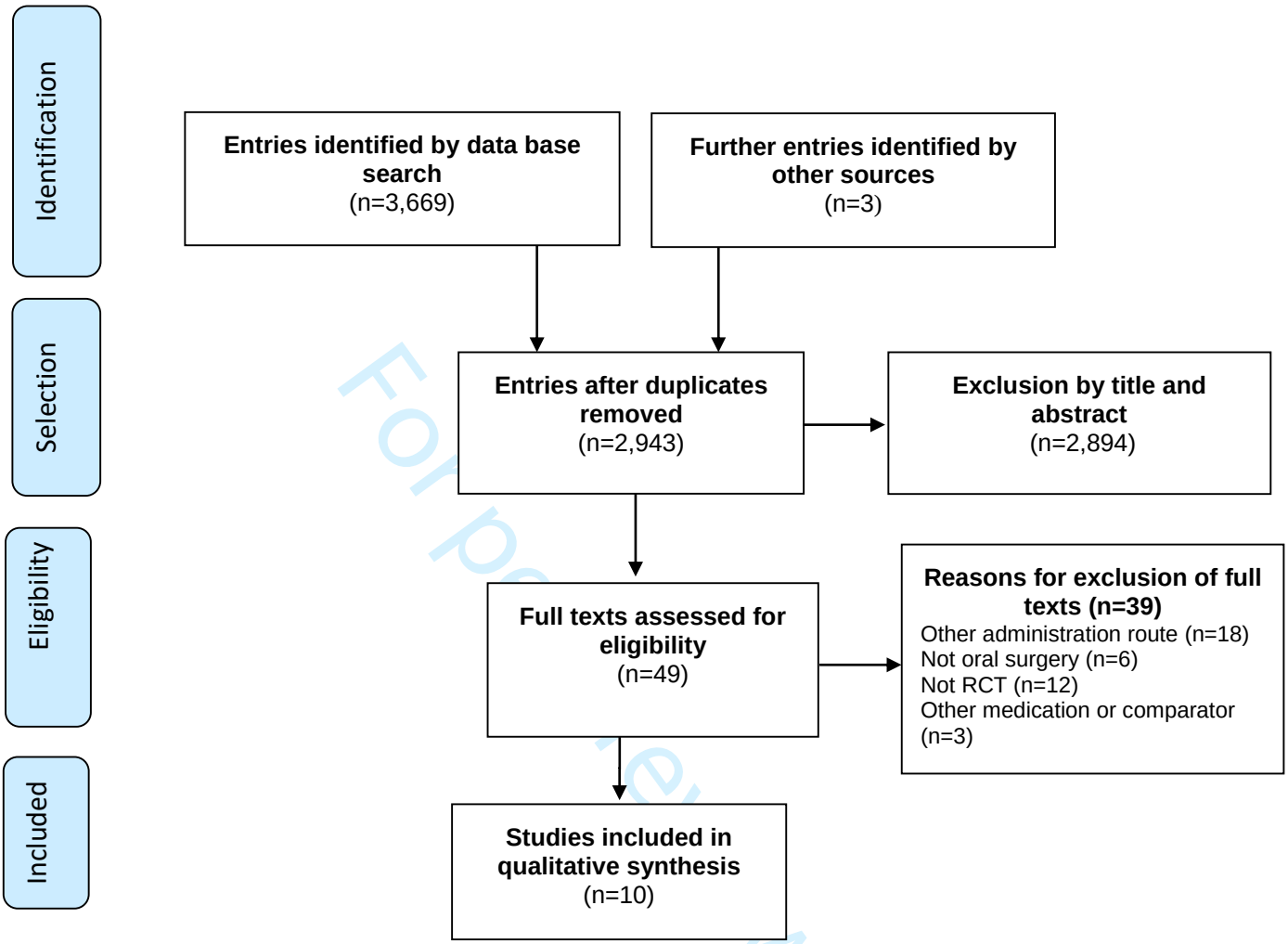

Figure 2 – Consensus of authors on risks of bias of the studies included

APPENDIX A – Search strategy on MEDLINE (via Ovid) database

1.	surgery, maxillofacial.mp. or exp Surgery, Oral/
2.	operative dentistry.mp. or exp Dentistry, Operative/
3.	dentistry, operative.mp. or exp Dentistry, Operative/
4.	prosthesis, surgical dental.mp. or Dental Implants/
5.	prostheses, surgical dental.mp. or exp Dental Implants/
6.	surgical dental prosthesis.mp. or exp Dental Implants/
7.	surgical dental prostheses.mp. or exp Dental Implants/
8.	dental prosthesis, surgical.mp. or exp Dental Implants/
9.	dental prostheses, surgical.mp. or exp Dental Implants/
10.	implant, dental.mp. or exp Dental Implants/
11.	dental implant.mp. or exp Dental Implants/
12.	implants, dental.mp. or exp Dental Implants/
13.	dental implants.mp. or exp Dental Implants/
14.	procedures, maxillofacial.mp. or exp Oral Surgical Procedures/
15.	procedure, maxillofacial.mp. or exp Oral Surgical Procedures/
16.	maxillofacial procedure.mp. or exp Oral Surgical Procedures/
17.	maxillofacial procedures.mp. or exp Oral Surgical Procedures/
18.	exodontics.mp. or exp Surgery, Oral/
19.	procedure, oral surgical.mp. or exp Oral Surgical Procedures/
20.	oral surgical procedure.mp. or exp Oral Surgical Procedures/
21.	surgical procedures, oral.mp. or exp Oral Surgical Procedures/
22.	procedures, oral surgical.mp. or exp Oral Surgical Procedures/
23.	surgical procedures, oral.mp. or exp Oral Surgical Procedures/
24.	oral surgical procedures.mp. or exp Oral Surgical Procedures/
25.	oral surgery.mp. or exp Surgery, Oral/
26.	maxillofacial surgery.mp. or exp Surgery, Oral/
27.	surgery, oral.mp. or exp Surgery, Oral/
28.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29.	benzodiazepinones.mp. or exp Benzodiazepinones/
30.	Benzodiazepinones.mp. or exp Benzodiazepinones/
31.	Alprazolam novopharm brand.mp. or expAlprazolam/
32.	novopharm brand of alprazolam.mp. or exp Alprazolam/
33.	novo alprazol.mp. or exp Alprazolam/
34.	novoalprazol.mp. or exp Alprazolam/
35.	novo-alprazol.mp. or exp Alprazolam/
36.	Alprazolam pfizer brand.mp. or exp Alprazolam/
37.	pfizer brand of alprazolam.mp. or exp Alprazolam/
38.	maleate, midazolam.mp. or exp Midazolam/
39.	midazolam maleate.mp. or exp Midazolam/
40.	midazolam.mp. or exp Midazolam/
41.	effect, antianxiety.mp. or exp Anti-Anxiety Agents/
42.	antianxiety effect.mp. or exp Anti-Anxiety Agents/
43.	effects, anti-anxiety.mp. or exp Anti-Anxiety Agents/
44.	anti anxiety effects.mp. or exp Anti-Anxiety Agents/
45.	anti-anxiety effects.mp. or exp Anti-Anxiety Agents/
46.	effect, anxiolytic.mp. or exp Anti-Anxiety Agents/
47.	anxiolytic effect.mp. or exp Anti-Anxiety Agents/

48.	effects, antianxiety.mp. or exp Anti-Anxiety Agents/
49.	antianxiety effects.mp. or exp Anti-Anxiety Agents/
50.	effects, anxiolytic.mp. or exp Anti-Anxiety Agents/
51.	anxiolytic effects.mp. or exp Anti-Anxiety Agents/
52.	effect, anti-anxiety.mp. or exp Anti-Anxiety Agents/
53.	anti anxiety effect.mp. or exp Anti-Anxiety Agents/
54.	anti-anxiety effect.mp. or exp Anti-Anxiety Agents/
55.	anxiolytics.mp. or exp Anti-Anxiety Agents/
56.	drugs, anti-anxiety.mp. or exp Anti-Anxiety Agents/
57.	anti anxiety drugs.mp. or exp Anti-Anxiety Agents/
58.	anti-anxiety drugs.mp. or exp Anti-Anxiety Agents/
59.	minor tranquillizing agents.mp. or exp Anti-Anxiety Agents/
60.	agents, minor tranquillizing.mp. or exp Anti-Anxiety Agents/
61.	minor tranquilizing agents.mp. or exp Anti-Anxiety Agents/
62.	agents, minor tranquilizing.mp. or exp Anti-Anxiety Agents/
63.	tranquilizing agents, minor.mp. or exp Anti-Anxiety Agents/
64.	agents, anxiolytic.mp. or exp Anti-Anxiety Agents/
65.	anxiolytic agents.mp. or exp Anti-Anxiety Agents/
66.	anti anxiety agents.mp. or exp Anti-Anxiety Agents/
67.	agents, anti-anxiety.mp. or exp Anti-Anxiety Agents/
68.	anti-anxiety agents.mp. or exp Anti-Anxiety Agents/
69.	29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68
70.	69 and 28

APPENDIX B – CHARACTERISTICS OF STUDIES INCLUDED

Study characteristics	**Branco & Bassualdo (2012)**
Method	Randomized double-blind placebo-controlled clinical trial. Allocated 30 participants undergoing dental implant placement surgery into 3 different groups (n=10) to receive a drug 1 hour before procedure. Group I – diazepam 10 mg; Group II – lorazepam 1 mg; Group III – placebo.
Participants	30 participants, both genders, mean age 20-64 years, selected for dental implant placement surgery.
Intervention	Three groups of patients underwent surgery for dental implant placement after oral sedation.
Outcomes	Primary outcomes: anxiety. Secondary outcomes: vital signs (blood pressure, heart rate).
Observations	There were no significant differences in reduction of anxiety or in vital signs pre and post-operatively, only trans-operatively. Effective anxiety control was not demonstrated.

Branco & Bassualdo (2012)	**Deemed risk of bias**	**Support for judgement**
Random sequence generation	High risk	Randomized, although no detailed report on procedure was provided in study description.
Allocation concealment	High risk	No information or scant description on procedures for concealing allocation of patients into groups.

Blinding of participants and personnel	Low risk	Blinding of participants and personnel was done, making it unlikely blinding was lost.
Blinding of outcome assessors	High risk	The study failed to report this information. The outcomes assessed are subject to influence by lack of blinding.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	Low risk	The study protocol is not available, but the study published clearly included all desired outcomes.
Other sources of bias	Low risk	The study appeared to have no other sources of bias.

Study characteristics	**Coldwell et al. (1997)**
Method	Allocated 48 participants undergoing oral surgery for dental extraction into 4 different groups (n=12). Group 1 – alprazolam 0.25 mg; Group 2 – alprazolam 0.50 mg; Group 3 – alprazolam 0.75 mg; Group 4 – placebo.
Participants	48 participants of both genders were selected for surgical dental extraction of 1-4 molars.
Intervention	Four groups of patients submitted to surgical dental extraction after oral sedation.
Outcomes	Primary outcomes: anxiety, adverse effect (anterograde amnesia).
Observations	The study showed that alprazolam caused memory impairment at doses necessary for producing clinically significant anxiolytic effect during oral surgery.

Coldwell et al. (1997)	**Deemed risk of bias**	**Support for judgement**
Random sequence generation	High risk	Randomized, although no detailed report on procedure was provided in study description.
Allocation concealment	High risk	No information or scant description on procedures for concealing allocation of patients into groups.
Blinding of participants and personnel	Low risk	Study not blinded or incomplete blinding, and outcome unaffected by lack of blinding.
Blinding of outcome assessors	High risk	The study failed to report this information. The outcomes assessed are subject to influence by lack of blinding.
Incomplete outcomes	High risk	Insufficient information to judge. The study did not report this information.
Selective outcome reporting	Low risk	The study protocol is not available, but the study published clearly included all desired outcomes.
Other sources of bias	High risk	Insufficient information to judge. The study did not report this information.

Study characteristics	**Dantas et al. (2017)**

Method	Randomized double-blind clinically-controlled crossover trial. Allocated 40 participants undergoing surgical extraction of third molars into 2 groups (n=40) receiving orally administered drug 30 mins before procedure. Group I – *Passiflora incarnata* 260 mg; Group II – midazolam 15 mg.
Participants	40 participants of both genders were selected for third molar extraction.
Intervention	Two groups of patients undergoing surgery for third molar extraction after oral sedation.
Outcomes	Primary outcomes: anxiety, adverse effects. Secondary outcomes: vital signs (blood pressure and heart rate) and oxygen saturation.
Observations	*Passiflora incarnata* promoted similar anxiolytic effect to midazolam, and participants who received the drug had relatively stable blood pressure, heart rate and oxygen saturation.

Dantas et al. (2017)	**Deemed risk of bias**	**Support for judgement**
Random sequence generation	High risk	Randomized, although no detailed report on procedure was provided in study description.
Allocation concealment	High risk	No information or scant description on procedures for concealing allocation of patients into groups.
Blinding of participants and personnel	Low risk	Blinding of participants and personnel was done, making it unlikely blinding was lost.
Blinding of outcome assessors	Low risk	Blinding of outcome assessors was done, making it unlikely blinding was lost.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	Low risk	The study protocol is not available, but the study published clearly included all desired outcomes.
Other sources of bias	Low risk	The study appeared to have no other sources of bias.

Study characteristics	**Manani et al. (1979)**
Method	Randomized double-blind clinically-controlled trial. Allocated 82 patients of both genders, age range 20-50 years, undergoing dental procedures into 4 groups according to drug administered for inducing sedation. Group I – placebo; Group II – trazodone 25 mg; Group III – trazodone 50 mg; Group IV – diazepam 15 mg.
Participants	82 participants of both genders, age range 20-50 years, selected for surgery with oral sedation.
Intervention	O Group I received placebo (Control Group). Group II received trazodone 25 mg. Group III received trazodone 50 mg. Group IV received diazepam 15 mg. All drugs were prepared and distributed in the form of blue capsules to prevent identification of Group by the participants and professionals.
Outcomes	Primary outcomes: anxiety, sedation, adverse effects (drowsiness, vertigo, headache, blurred vision, cold hands and dry mouth). Secondary outcomes: vital signs (blood pressure and heart rate).
Observations	One hour after administration of drug, there was a significant increase in sedation of patients. No adverse effects were observed in patients of control group or trazodone 25 mg group. Patients using diazepam 15 mg or trazodone 50 mg had greater reduction in

	neurovegetative response and higher rate of adverse effects, proving more marked in the group treated with diazepam.

Manani et al. (1979)	**Deemed risk of bias**	**Support for judgement**
Random sequence generation	High risk	Insufficient information on random sequence generation process to allow judgement. No detailed report on procedure was provided in study description.
Allocation concealment	High risk	No information or scant description on procedures for concealing allocation of patients into groups.
Blinding of participants and personnel	Low risk	The study stated that all drugs were placed into identical capsules, thereby ensuring blinding of participants and personnel.
Blinding of outcome assessors	High risk	The study failed to report this information. The outcomes assessed are subject to influence by lack of blinding.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	Low risk	The study protocol is not available, but the study published clearly included all desired outcomes.
Other sources of bias	Low risk	The study appeared to have no other sources of bias.

Study characteristics	**Rodrigo & Cheung (1987)**
Method	Randomized double-blind clinical trial. Allocated 30 participants undergoing surgical extraction of mandibular third molars to receive orally administered drug midazolam 15 mg or placebo, the surgery was carried out by a single operator, randomly, one side per visit.
Participants	30 participants of both genders were selected for surgical removal of third molars.
Intervention	The patients underwent surgical removal of third molars after oral sedation.
Outcomes	Primary outcomes: adverse effects (amnesia, hiccupping, nausea, drowsiness and dizziness) and satisfaction with treatment.
Observations	Midazolam sedation lasted about 45 minutes, produced good operating conditions and stable vital signs with adequate verbal response.

Rodrigo & Cheung (1987)	**Deemed risk of bias**	**Support for judgement**
Random sequence generation	High risk	Randomized, although no detailed report on procedure was provided in study description.

Allocation concealment	Low risk	The pills were sealed and coded in envelopes and thus information on procedures confirmed concealment of allocation of patients into groups.
Blinding of participants and personnel	Low risk	Blinding of participants and personnel was incomplete, but the authors claimed outcome was unaffected by the lack of blinding.
Blinding of outcome assessors	Low risk	Blinding of outcome assessors was done, making it unlikely blinding was lost.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	High risk	Study protocol not available and there was insufficient information to allow judgement.
Other sources of bias	Low risk	The study appeared to have no other sources of bias.

Study characteristics	**Pinheiro et al. (2014)**
Method	Randomized double-blind clinically-controlled study. Allocated 20 participants undergoing bilateral extraction of third molars into 2 groups (n=10) orally administered drug 1 hour before procedure. Group I – *Valeriana officinalis* 100 mg; Group II – placebo.
Participants	20 Participants aged 17-31 years of both genders were selected for bilateral extraction of impacted third lower molars.
Intervention	Two patient groups underwent surgery for extraction of third molars after oral sedation.
Outcomes	Primary outcomes: anxiety, adverse effects (drowsiness, fear and muscle relaxation). Secondary outcomes: vital signs (systolic and diastolic blood pressure, heart rate).
Observations	Pre-operative dose of *Valeriana officinalis* had greater anti-anxiety effect than placebo.

Pinheiro et al. (2014)	**Deemed risk of bias**	**Support for judgement**
Random sequence generation	Low risk	Medications with the same concentrations, size and appearance were placed in envelopes, thus there was sufficient information on the method used for random sequence generation.
Allocation concealment	High risk	Insufficient information on random sequence generation process to allow judgement. It was stated that envelopes were used, but it remained unclear whether these were sealed, opaque or numbered sequentially.
Blinding of participants and personnel	Low risk	Blinding of participants and personnel was done, making it unlikely blinding was lost.
Blinding of outcome assessors	High risk	Insufficient information to judge. The study did not report this information.
Incomplete outcomes	Low risk	There was no loss of outcome data.

Selective outcome reporting	Low risk	The study protocol was available and all pre-specified primary and secondary outcomes of interest in the review were reported as proposed.
Other sources of bias	Low risk	The study appeared to have no other sources of bias.

Study characteristics	**Romano et al. (2011)**
Method	Randomized double-blind clinical trial. Allocated 15 participants undergoing dental implant were orally administered the drug midazolam 15 mg or placebo 1 hour before the procedure. The surgery was carried out by the same operator in 2 surgical visits with 30-day interval between sessions.
Participants	15 participants age 21-50 years of both genders were selected for dental implant placement.
Intervention	Two patient groups underwent surgery for dental implant placement after oral sedation.
Outcomes	Secondary outcomes: vital signs (heart rate).
Observations	No difference for use of 15 mg midazolam versus placebo, with no advantage for incidence of arrhythmias. Anxiolytic premedication failed to prevent arrhythmia.

Romano et al. (2011)	**Deemed risk of bias**	**Support for judgement**
Random sequence generation	High risk	There was insufficient information on procedures for concealing allocation of patients into groups.
Allocation concealment	Low risk	It was stated that envelopes were sealed, providing information on procedures concealing allocation of patients into groups.
Blinding of participants and personnel	Low risk	Blinding of participants and personnel was done, making it unlikely blinding was lost.
Blinding of outcome assessors	High risk	Insufficient information to judge. The study did not report this information.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	Low risk	The study protocol is not available, but the study published clearly included all desired outcomes.
Other sources of bias	High risk	Insufficient information to assess whether there was relevant risk of bias.

Study characteristics	**Silveira-Souto et al. (2014)**
Method	Randomized double-blind crossover clinical study. Allocated 30 participants undergoing surgery for extraction of third

	molars to receive orally administered medication *E. mulungu* 500 mg or placebo, 1 hour before procedure, at first or second surgical intervention, left or right side, compared to placebo group.
Participants	30 participants of both genders were selected for extraction of third molars.
Intervention	Patients underwent surgery for extraction of third molars after oral sedation.
Outcomes	Primary outcomes: anxiety and satisfaction with treatment. Secondary outcomes: vital signs (blood pressure) and oxygen saturation.
Observations	*E. mulungu* can be considered a viable alternative, having produced no meaningful changes in physiological parameters (respiratory depression or motor abnormalities).

Silveira-Souto et al. (2014)	**Deemed risk of bias**	**Support for judgement**
Random sequence generation	Low risk	Randomization was performed using randomized computer-generated numbers, thus there was sufficient information about the method used for generating the random sequence.
Allocation concealment	Low risk	Information was given on procedures for concealing allocation of patients into groups, through coding in protocols
Blinding of participants and personnel	Low risk	Blinding of participants and personnel was done, making it unlikely blinding was lost.
Blinding of outcome assessors	Low risk	Blinding of outcome assessors was done, making it unlikely blinding was lost.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	Low risk	The study protocol is not available, but the study published clearly included all desired outcomes.
Other sources of bias	Low risk	The study appeared to have no other sources of bias.

Study characteristics	**Studer et al. (2012)**
Method	Randomized double-blind crossover study. Allocated 12 participants undergoing surgery for bilateral extraction of third molars to receive drug orally administered 1 hour before procedure. Group I – midazolam 7.5 mg; Group II – clonidine 150 ug. The procedure was performed by the same dental surgeon during two surgical visits with follow-up of 7 days.
Participants	12 participants of both genders were selected for bilateral extraction of third molars.
Intervention	The patients underwent surgery for extraction of third molars after oral sedation.
Outcomes	Primary outcomes: anxiety, adverse effects (dizziness, nausea, headache, fatigue, metallic taste and concentration difficulties. Secondary outcomes: satisfaction with treatment.
Observations	The two medications were rated similar for patient satisfaction. Oral administration of clonidine 150 ug and midazolam 7.5 mg

	medications promoted similar anxiolytic effects before surgery with local anaesthesia.

Studer et al. (2012)	**Deemed risk of bias**	**Support for judgement**
Random sequence generation	Low risk	Randomization was performed using randomized computer-generated list, thus there was sufficient information about the method used for generating the random sequence.
Allocation concealment	High risk	No information or scant description on procedures for concealing allocation of patients into groups.
Blinding of participants and personnel	Low risk	Blinding of participants and personnel was done, making it unlikely blinding was lost.
Blinding of outcome assessors	High risk	The study failed to report this information. Outcomes assessed were subject to influence by the lack of blinding.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	Low risk	The study is not available, but the study published clearly included all the desired outcomes.
Other sources of bias	High risk	Insufficient information to assess whether there was relevant risk of bias.

Characteristics of studies	**Shivananda et al. (2014)**
Method	Randomized double-blind crossover clinical trial. Allocated 20 participants undergoing periodontal surgery. Twenty subjects requiring minimum 2 sextants of flap surgery were selected for the study. Each sextant was randomly assigned into experimental and control sites.
Participants	20 participants of both genders were selected for periodontal surgery, experimental group under 68 kg received diazepam 5 mg and over 68 kg 10 mg - the night before and 1 hour before surgery.
Intervention	Modified widman flap surgery was performed in experimental site with pre-operative oral diazepam sedation and local anaesthesia. Similar surgery was performed in the control site with pre-operative oral placebo and using local anaesthesia only.
Outcomes	Secondary outcomes: oxygen saturation
Observations	There was no statistically significant difference between sedated and non-sedated patients for oxygen saturation. Oral conscious sedation can be used for anxious patients during periodontal surgery for alleviation of anxiety and for better patient acceptance during surgical procedures without significant respiratory depression.

Shivananda et al. (2014)	**Deemed risk of bias**	**Support for judgement**
Random sequence generation	High risk	There was insufficient information on procedure concealing allocation of patients into groups.

Allocation concealment	High risk	No information or scant description on procedures for concealing allocation of patients into groups.
Blinding of participants and personnel	Low risk	Blinding of participants and personnel was done, making it unlikely blinding was lost.
Blinding of outcome assessors	High risk	The study failed to report this information. Outcomes assessed were subject to influence by lack of blinding.
Incomplete outcomes	Low risk	There was no loss of outcome data.
Selective outcome reporting	High risk	The study protocol was not available, thus there was insufficient information to allow judgement.
Other sources of bias	Low risk	The study appeared to have no other sources of bias.

APPENDIX C – LIST OF EXCLUDED STUDIES AND MAIN REASONS FOR EXCLUSION

Other administration route	1. Barclay JK, Hunter KM, Jones H. Diazepam and lorazepam compared as sedatives for out patient third molar surgery. British Journal of Oral Surgery. 1980;18:141-149. 2. Bavisha KA, Elias M, Paris S, Leon AR, Flynn PJ. Comparison of patient-controlled and operator-controlled conscious sedation for restorative dentistry. European Journal of Anaesthesiology. 2004;21:284-288. 3. Cheung CW, Ying CLA, Chiu WK, Wong GTC, Ng KFJ, Irwin MG. A comparison of dexmedetomidine and midazolam for sedation in third molar surgery. Anaesthesia. 2007;62:1132-1138. 4. Fan TWV, Ti LK, Islam I. Comparison of dexmedetomidine and midazolam for conscious sedation in dental surgery monitored by bispectral índex. British Journal of Oral and Maxillofacial Surgery. 2013;51:428-433. 5. Hosie HE, Brook IM, Nimmo WS. Comparison of sedation with temazepam by mouth and diazemuls I.V. for dental surgery. Br J Anaesth. 1988;60:18-23. 6. Luyk NH, Whitley BD. Efficacy of oral midazolam prior to intravenous sedation for there moval of third molars. Int J Oral Maxillofac Surg. 1991;20:264-267. 7. Ochs MW, Tucker MR, White RP, Anderson JA. Recovery following sedation with midazolam or diazepam alone or in combination with fentanyl for out patient surgery. Anesthesia Progress. 1986;230-234. 8. Osborne GA, Rudkin GE, Curtis NJ, Vickers D, Craker AJ. Intra-operative patient-controlled sedation. Anaesthesia. 1991;46:553-556. 9. Rodrigo MRC, Tong CKA. A comparison of patient and anasthetist controlled midazolam sedation for dental surgery. Anaesthesia. 1994;49:241-244. 10. Richmond MN, Daum REO. Premedication with oral slow release morphine in dental anaesthesia: A comparison with temazepam. Anaesthesia. 1988;43:694-696. 11. Stopperich PS, Moore PA, Finder RL, McGirl BE, Weyant RJ. Oral triazolam pretreatment for intravenous sedation. Anesth Prog. 1993;40:117-121.

	12. Rubim J, Schweggmann I, Uys P. Lorazepam as a premedicant in dental surgery. S AfrMed J. 1980;58(3):124-126. 13. Mohamad EM. Midazolam versus but or phanolaslocal an anesthetic adjuncts in oral surgery: a clinical assessment. Egyptian Dental Journal. 1987;33(4):363-374. 14. Zanette G, Manani G, Favero L, Stellini E, Mazzoleni S, Cocilovo F, et al. Conscious sedation with Diazepam and midazolam for dental patient: priority to diazepam. Minerva Stomatol. 2013;62:355-374. 15. Manani G, Baldinelli L, Cordioli G, Consolati E, Luisetto F, Galzigna L. Premedication with Chlordemethyldiazepam and anxiolytic effect of diazepam in implantology. AnesthProg. 1995;42:107-112. 16. Lieblich SE, Horswell B. Attenuation of anxiety in ambulatory oral surgery patients with oral triazolam. J Oral Maxillofac Surg. 1991;49:792-795. 17. Luyk NH, Weaver JM, Beck FM, Loetscher CA, Sacks J. The effectiveness of flurazepam as night sedation prior to there moval of third molars. Int J Oral Maxillofac Surg. 1988;17:347-351. **18.** O'Boyle CA, et al. Comparison of midazolam by mouth and diazepam I.V. in out patient oral surgery. Br J Anaesth. 1987;59:746.
Not oral surgery	19. Ahmed N, Khan FA. Evaluation of oral midazolam as pre-medication in day care surgery in adult Pakistani patients. J Pak Med Assoc. 1995;45(9):239-241. 20. Hargreaves J. Benzodiazepine premedication in minorday-case surgery: comparison of oral midazolam and temazepam with placebo. Br J Anaesth. 1988; 61:611-616. 21. Patel T, Kurdi MS. A comparative study between oral melatonin and oral midazolam on preoperative anxiety, cognitive, and psychomotor functions. Journal of Anaesthesiology Clinical Pharmacology. 2015;31(1):37-43. 22. Baird ES, Curson I. Orally administered diazepam in conservative dentistry. British Dental Journal. 1970;128:25-27. 23. Irjala J, Kanto J, Irjala K, Salonen M, Viinamaki O. Temazepam versus flunitrazepam as na oral premedication in adult surgical patients. European Journal of Anesthesiology. 1987;4:435-440. 24. Raybould D, Bradshaw EG. Premedication for day case surgery: a study of oral midazolam. Anaesthesia. 1987;42:591.
Not RCT (n=12)	25. Johren P, Jackowski J, Gangler P, Sartory G, Thom A. Fear reduction in patients with dental treatment phobia. British Journal of Oral and Maxillofacial Surgery. 2000;38:612-616. 26. Ochs MW, Tucker MR, White RP. A comparison of amnesia in outpatients sedated with midazolam or diazepam alone or in combination with fentanyl during oral surgery. JADA. 1986;113:894-897. 27. Khosla VM, Boren W. Diazepam (Valium) as preoperative medication in oral surgery. Anesthesiology. 1969;28(5):671-679. 28. Debernardi G, Debernardi C. Sperimentazione clinicasull'azione di una benzodiazepine (Lexotan) sulcomportamento del paziente ansiosonell'ambulatorio odonto stomatologico. Min Stom. 1985; 34:323-328. 29. Noguchi T, Hayano Y, Iwasaka H, Miyamoto M, Habu A, Tsuzaki K, et al. A study of clinical efficacy of triazolam as preanesthetic medication. 1985;34(4):493-499. 30. Shane SM, Baltimore. Amnesia for brief exodontia procedures using small doses of diazepam and methohexital with local block anesthesia for ambulatory patients. J Oral Surgery. 1971;29:191-193. 31. Skelly AM, Boscoe MJ, Dawling S, Adams AP. A comparison of diazepam and midazolam as sedatives for minor oral surgery. European Journal of Anaesthesiology. 1984;(1):253-267.

	32. Wahlmann UW, Dietrich U, Fischer W. Zurfrage der oral em sedierung mit midazolam bei ambulante zahnarztlich-chirurgischen eingriffen. Disch Zahnarztl Z. 1992;47:66-68. 33. Reinhardt LC, Felberg RV, Lemes CHJ. Comparative study of bone response guided tissue regeneration clinical evaluation of the anxiety and cardiovascular parameters with the use of anxiolitic in the pre-operative in bucomaxilofacial surgery. Full Dentistry in Science. 2010;1(4):328-331. 34. Aeschliman SD, Blue MS, Williams KB, Cobb CM, MacNeill SR. A preliminary study on oxygen saturation levels of patients during periodontal surgery with and without oral conscious sedation using diazepam. J Periodontol. 2003;74(7):1056-1059. 35. Moorthi RK, Kumar MPS. Pre- and post-operative anxiety in patients undergoing dental extractions. Drug Ivention Today. 2018;10(12):2445-2449. 36. James D, Nazar N. Role of anti- anxiety drugs patient cooperation during minor surgical procedure. Research J. Pharm. and Tech.2018; 11(8): 3389-3391
Other medication or comparator	37. Kanto D, Salo M, Happonen RP, Vahlberg T, Kanto J. Tramadol premedication in operative extraction of the mandibular third molar: a placebo-controlled crossover study. Acta Odontologica Scandinavica. 2005; 63:43-49. 38. White CS, Dolwick MF, Gravenstein N, Paulus DA. Incidence of oxygen desaturation during oral surgery out patient procedures. J Oral Maxillofac Surg. 1989;47:147-149. 39. Dellovo AG, Souza LMA, Oliveira JS, Amorim KS, Groppo FC. Effects of auriculotherapy and midazolam for anxiety control in patients submitted to third molar extraction. Int J Oral Maxillofac Surg. 2018;18:1-6.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7,8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8, Appendix A
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8,9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5, 7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (I^2) for each meta-analysis.	10

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10,11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11,12,13 and Appendix B
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14 to 22
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	22 to 24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	24,25
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	26
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	26

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Synthesis Without Meta-analysis (SWiM) reporting items

The citation for the Synthesis Without Meta-analysis explanation and elaboration article is: Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, Hartmann-Boyce J, Ryan R, Shepperd S, Thomas J, Welch V, Thomson H. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline BMJ 2020;368:l6890 http://dx.doi.org/10.1136/bmj.l6890

SWiM is intended to complement and be used as an extension to PRISMA			
SWiM reporting item	**Item description**	**Page in manuscript where item is reported**	**Other***
Methods			
1 Grouping studies for synthesis	1a) Provide a description of, and rationale for, the groups used in the synthesis (e.g., grouping by populations, interventions, outcomes, study design)	***6***	
	1b) Detail and provide rationale for any changes made subsequent to the protocol in the groups used in the synthesis	***Not applicable***	
2 Describe the standardised metric and transformation methods used	Describe the standardised metric for each outcome. Explain why the metric(s) was chosen, and describe any methods used to transform the intervention effects, as reported in the study, to the standardised metric, citing any methodological guidance consulted	***7***	
3 Describe the synthesis methods	Describe and justify the methods used to synthesise the effects for each outcome when it was not possible to undertake a meta-analysis of effect estimates	***10***	
4 Criteria used to prioritise results for summary and synthesis	Where applicable, provide the criteria used, with supporting justification, to select the particular studies, or a particular study, for the main synthesis or to draw conclusions from the synthesis (e.g., based on study design, risk of bias assessments, directness in relation to the review question)	***Not applicable***	

Synthesis Without Meta-analysis (SWiM) reporting items

SWiM reporting item	Item description	*Page in manuscript where item is reported*	Other*
5 Investigation of heterogeneity in reported effects	State the method(s) used to examine heterogeneity in reported effects when it was not possible to undertake a meta-analysis of effect estimates and its extensions to investigate heterogeneity	***10***	
6 Certainty of evidence	Describe the methods used to assess certainty of the synthesis findings	***9-10***	
7 Data presentation methods	Describe the graphical and tabular methods used to present the effects (e.g., tables, forest plots, harvest plots). Specify key study characteristics (e.g., study design, risk of bias) used to order the studies, in the text and any tables or graphs, clearly referencing the studies included	***9-10***	
	Results		
8 Reporting results	For each comparison and outcome, provide a description of the synthesised findings, and the certainty of the findings. Describe the result in language that is consistent with the question the synthesis addresses, and indicate which studies contribute to the synthesis	***13-16***	
Discussion			
9 Limitations of the synthesis	Report the limitations of the synthesis methods used and/or the groupings used in the synthesis, and how these affect the conclusions that can be drawn in relation to the original review question.	***22***	

PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
*If the information is not provided in the systematic review, give details of where this information is available (e.g., protocol, other published papers (provide citation details), or website (provide the URL)).